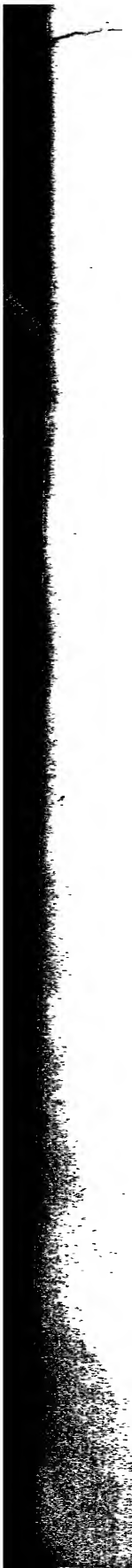
COLLECTED PAPERS ON BERIBERI



COLLECTED PAPERS ON BERIBERI.

STUDIES FROM THE INSTITUTE FOR MEDICAL RESEARCH, FEDERATED MALAY STATES.

No. 17.

COLLECTED PAPERS ON BERI-BERI

BY

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PREFACE.

THE papers reproduced in this volume have been selected from the contributions made by the authors from 1907 onwards to the study of beriberi in Malaya.

In the abundant literature which is gathering about the subject of vitamins, it is rare to find any adequate presentation of the facts elucidated in earlier studies on human diseases such as beriberi. We venture, therefore, to republish our observations in collected form in the hope that later students of this group of diseases may find in them something of interest.

Two lines of research independently pursued have contributed to the evolution of the order of ideas connoted by the terms "vitamins," "accessory food factors," and "deficiency diseases"; on the one hand researches into the causation of human diseases, and on the other hand researches in connection with problems of animal nutrition. These researches have proved to be complementary, and in the result important additions have been made to knowledge in physiology and in disease prevention.

When our inquiries were begun in 1907, current views of the etiology of beriberi were: (*a*) that it was a microbial infectious disease; (*b*) that it was due to nitrogen starvation; (*c*) that it was caused by a toxin the product of a saprophyte outside the human body. More than fifty years earlier suggestions had been put forward assigning to a rice diet the origin of the disease, and the experimental work of Eijkman and Grijns in Java, and the observations of Braddon in Malaya had been recorded in numerous publications from 1897 onwards. But no conviction had been brought to the minds of students of beriberi either in Europe or in the countries where these views were promulgated. For fifteen years later beriberi continued to ravage the countries of the Far East. It was regarded as a mysterious malady which had defied the efforts of investigators.

It was necessary then for us to begin our inquiries by experiments to test whether there was any connection whatever between a rice diet and beriberi. In 1907-1908 we carried out a series of such experiments under conditions which excluded or adequately controlled the factor of infection. In these experiments it was proved: (1) that beriberi was not communicable from man to man either through direct contact or through the intermediary of ectoparasites; (2) that place *per se* or considered as a nidus of infection played no part in its causation; and (3) that the disease has an intimate relation to diet.

Pursuing these inquiries in the laboratory with specimens of the rices used

in the earlier human experiments, we showed by studies on the structure of the rice grain and by animal feeding experiments that beriberi was not caused by a pre-formed poison ingested with rice, but that its origin was to be sought in a dietary defect. In 1910 we were able to say on evidence derived from a continuous series of experiments on man and animals that beriberi is a disorder of metabolism, and that white (polished or over-milled) rice as a staple of the diet is defective in alcohol-soluble substances, minute in amount, but of high physiological value in nutrition.

Concurrently with our inquiries, biochemical researches were in progress in Europe and America in connection with problems of animal nutrition. In 1906 Professor Gowland Hopkins foresaw "that developments of the science of dietetics will deal with factors highly complex and at present unknown;" and in 1912 he published the results of studies which proved the truth of his prophecy. Funk in 1912 began his studies with the "alcohol-soluble curative fraction" of rice-meal. He succeeded in precipitating the curative substances from solution and, thinking that he had isolated the substance in a chemically pure state, gave it the name "vitamine."

The application in practice of the scientific principles evolved by these researches has been attended by a notable success. Beriberi, which was formerly a scourge in the Orient, is now well on the way to extinction.

In reprinting these papers we have nowhere altered the sense of the text. Numerous verbal changes have been made consequent upon the omission of diagrams, and in an endeavour to clarify the meaning. Our thanks are due to the Editors of *The Lancet* and the *Philippine Journal of Science* for permission to republish papers which originally appeared in these journals.

January, 1923.

H. F.
A. T. S.

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ORIGINALLY PUBLISHED.

COLLECTED PAPERS ON BERIBERI.

Studies from the Institute for Medical Research, No. 10, 1909.

An Inquiry concerning the Etiology of Beriberi.

IT has long been recognized that the incidence of beriberi is greatest among rice eating peoples, and though from time to time a connection between a rice diet and this disease has been suggested, hypotheses based on such suggestions have not met with general acceptance. Indeed most authorities have deemed them unworthy of serious consideration.

Certain oriental peoples partake of a diet in which rice bulks very largely; meats and fish are eaten in relatively small amounts and in times of stress they are still further reduced. In view of this fact some observers have suggested that these people are underfed and that beriberi is the result of protein or possibly fat starvation.

Believing that the diet issued to the sailors in the Japanese Navy was deficient in protein, Takaki (1884) introduced dietetic reforms. These reforms were followed by a remarkable diminution in the number of cases and finally by the disappearance of the disease. Critics of Takaki's work have stated that, coincident with the alterations in diet, various sanitary reforms were also carried out and that these latter rather than the dietary changes were responsible for the results obtained.

Eijkman (1895), as the result of experiments on fowls concluded that there exists commonly in rice a poison which produces polyneuritis, and that for this poison or its effects something contained in the pericarp is an antidote.

An investigation based on the results of Eijkman's researches was carried out by Vordermann (1897) in the prisons of Java and Madoera. In this investigation red and white rices were used. The difference between red and white rice is that in the former only the husk has been removed, whilst in the latter the pericarp, embryo, spermoderm, perisperm and part of the endosperm have been removed. The results of the investigation showed that the incidence of beriberi among the prisoners varied directly as the amount of white rice in the diet. Among those on red rice the incidence of beriberi was ·01 per mille, among those on a mixture of red rice and white rice 2·4 per mille, and among those on white rice 28 per mille.

Braddon (1901; 1907), from observations in the Federated Malay States, has drawn attention to a curious inequality in the prevalence of beriberi among the immigrant peoples in Malaya, the vast majority of cases being met with in Chinese and extremely few among Tamils. He believes that the disease is due to the consumption of stale white rice, the staple article of diet among the Chinese immigrants, and that the Tamils remain free from the disease so long as they consume only rice prepared in the Indian manner, that is by parboiling before husking. A similar immunity from the disease enjoyed by Malays under primitive conditions he believes to be due to the fact that they consume rice prepared from padi newly husked. He has given the names "uncured," "cured" and "fresh" respectively to these forms of rice. This view of the etiology of beriberi is, if correct, an important advance upon any of the hypotheses hitherto formulated which seek for the origin of the disease in food. Braddon has dealt with the whole question in some detail in a recent publication, "The Cause and Prevention of Beriberi" and among the conclusions arrived at from an analysis of his own observations and the available statistical evidence are the following:—

(1) "The formation of poison in stale rice is probably due neither to fermentation nor bacteria but to the growth in it of a special fungus."

(2) "The poison of stale rice has an antecedent in fresh rice. The agent must be, therefore, some ferment or parasite or epiphyte peculiar to padi."

(3) "The specific fungus of beriberi is like that of toxic rye and lolium probably a parasite affecting the surface of the seed."

(4) "The beriberi producing fungus of rice is probably a surface parasite or epiphyte affecting the seed saprophytically after decortication."

(5) "The beriberi poison is probably an alkaloid which is stable and non-volatile and resembles atropine in some and muscarine in other of its effects."

Dubruel (1905) in a monograph "Le Béribéri," gives the results of his observations on the disease in French Indo-China, and concludes that beriberi is due to a pathogenic microbe developing in white rice which has been decorticated for some time. He believes that this pathogenic microbe taken with the rice produces an initial lesion in the alimentary canal, the other lesions characteristic of the disease following. He has not been able to isolate the supposed organism.

Van Dieren (1907) in a recent volume "Meelvergiftigingen" calls attention to the points of similarity, clinical and pathological, displayed by beriberi, pellagra, lathyrism and ergotism and concludes that these diseases are forms of grain poisoning.

Numerous micro-organisms have been recorded as occurring in cases of beriberi and by their discoverers have been held to be the causative agents. Satisfactory evidence in support of these claims has not yet been forthcoming.

Certain other authorities while admitting that there is no proof that the disease is bacterial or protozoal in origin hold that the balance of evidence is in favour of such a view.

Rice.

Rice furnishes daily food for more human beings than any other cereal. It is the chief product in China, Indo-China, Japan and other oriental countries. In the Federated Malay States and the Straits Settlements, the amount of rice grown is not great. Its cultivation is for the most part confined to Malays and save in Perak and Province Wellesley the amount grown only suffices for the needs of the cultivators, who store the grain in bins and husk it as required. To meet the requirements of a large and increasing number of immigrants, mainly natives of China and India, a very large amount of rice must be imported annually.

Padi, the grains of the rice plant, consists of the fruit enclosed in the paleæ which form the husk. The fruit possesses a thin pericarp firmly adherent to the seed and either silver-like or varying from dark red to black in colour. At the base of the dorsal edge may be seen the embryo lying in a depression. Subjacent to the pericarp are the spermoderm and the perisperm which surround the endosperm. The cells in the outer layers of the endosperm are filled with aleurone granules and the central portion of the seed is made up of cells closely packed with starch granules. Fat is practically confined to the outer layers of the seed.

In the preparation of rice from padi the product varies in accordance with the methods employed.

Malay Rice.

Malays who grow padi employ primitive methods; they pound the grains until the husks are detached and remove them by winnowing. Portions of the pericarp at least and perhaps all of it are removed; should the pericarp be coloured it is almost certain to be wholly removed, especially with careful housewives to whom this work is relegated, and whose chief desire is to prepare a *white* rice. The layers subjacent to the pericarp are not interfered with to the same extent as when the grains are milled and polished by machinery.

White Rice.

Imported rice, other than that from India and Sumatra, may be described as white rice and is the kind preferred by the immigrant peoples except Tamils, as well as by the Malays resident in towns. In accordance with the market requirements, imported padi is milled either into this rice or parboiled rice.

White rice is the "stale uncured" rice of Braddon and is the variety believed by him to be the source of the causative agent of beriberi.

For the preparation of this form of rice large mills have been established in the countries from which the rice is exported, also in Penang, Singapore,

and Malaya. In these mills padi is husked and polished by machinery and, since the demand is for a white rice, milling is carried out so thoroughly that in addition to the husk, pericarp, spermoderm and perisperm, a portion of the endosperm is removed; in consequence, the finished product consists almost wholly of cells closely packed with starch granules.

Parboiled Rice.

The Tamil labourer prefers a rice similar to that consumed by him in India, and a small amount of such rice is imported from India and Sumatra, but as the cost is considerably greater than that of white rice, its use is limited to the more wealthy Tamils and to some institutions. To meet the demand for a similar rice and to supply it at cheaper rates, padi is imported from the Siamese Malay States, Perak, and Province Wellesley and specially prepared in the mills of Penang and Singapore.

The padi is placed in large concrete tanks, covered with water, and soaked for about forty-eight hours. The moist padi is then transferred to lightly covered cylinders through which steam is passed for five minutes. Thereafter the padi is removed to paved courts and dried by exposure to the sun. It is then either stored as padi or milled at once.

The milling and polishing process is identical with that employed in the preparation of white rice but the endosperm is not interfered with to the same extent and consequently the aleurone layer is for the most part preserved. In microscopic sections of parboiled rice fragments of the pericarp may be seen.

As compared with similar rices imported from India and Sumatra the local product has a peculiar disagreeable odour which can to some extent be removed by careful washing previous to cooking. The exact cause of this difference has not been determined. These rices are here called parboiled rice (the "cured" rice of Braddon). The grains are yellowish and more or less translucent, and it may be that as this rice cannot be made white the polishing is carried to a less degree, or the treatment previous to milling may have rendered the peripheral layers less friable and thus less readily removed by polishing.

Comparison microscopically of Malay, parboiled and white rices shows that the latter has been deprived to the greatest extent of its oil-containing and aleurone layers. Chemically we have shown that parboiled rice contains relatively much more oil than white rice.

Feeding Experiments.

The investigations hereinafter described were undertaken primarily to determine if, when other factors were excluded or controlled, people fed on white rice developed beriberi, and if another group under exactly similar conditions, but fed on parboiled rice, did not develop the disease. It was hoped also that opportunity would be forthcoming for the investigation of other aspects of the question, such as the part played by infection.

At the outset it is necessary to state that the disease under investigation is

that form of multiple peripheral neuritis, known as beriberi, which occurs endemically in this peninsula and the neighbouring islands. As much confusion has been caused by assigning this name to classes of cases differing widely in their clinical manifestations, it is desirable to make it clear that we seek only for an explanation of this disease as met with here.

For the purpose of the inquiry it was necessary to have two parties of men under similar conditions as to environment and whose food supply was definitely known. In view of the suggestion that the disease may be bacterial or protozoal in origin it was desirable also that the places chosen should have been hitherto uninhabited or that no case of beriberi should have occurred there for some time previously; further, the places should be in an isolated district, sufficiently remote from towns or villages to exclude as far as possible the entrance of a supposed infection. Such a situation would also have the advantage, on account of the absence of shops, that the men under observation could not readily obtain food other than that supplied to them.

It is obvious that the conditions required for such an investigation could not be secured in a public institution, as in all such institutions in Malaya beriberi is known to be endemic. Various places were visited with a view to securing satisfactory conditions, and it was finally decided that the subjects of experiment should be some three hundred Javanese indentured labourers employed in the work of road construction in a remote part of the Jelebu district in the State of Negri Sembilan. The places in which the labourers were at this time employed, Kuala Ayer Baning and Durian Tipus, were sufficiently remote from the nearest village or town for the purpose and Malay settlements in the district were few in number and small in size. In connection with these latter it should be remembered that abundant evidence exists to show that Malays in such situations do not suffer from beriberi.

Previous Medical History of the Groups.

The first indentured Javanese coolies employed on road construction in the Jelebu district commenced work at Pesasi in March 1905. At that time only a small number of Javanese was employed and during the year following they were moved to Pertang. In September 1906, the work having been completed, many of the labourers were sent further along the road and occupied quarters newly erected at Kuala Ayer Baning, and in January 1907 quarters newly erected were occupied at Durian Tipus. By the end of 1906 the number of Javanese employed had been largely increased and then numbered about four hundred.

Under the terms of contract the rice issued to these labourers was supplied by the contractor and, as they prefer white rice, this kind was supplied. In the early months of 1906 a number of cases of beriberi occurred among them and in May, June and July of that year it was a serious source of invaliding and mortality. From August 2, 1906, the employer, adopting the suggestion of Dr. Braddon, issued only parboiled rice instead of white rice; thenceforward it is stated, and this statement is confirmed by the hospital records, no case of beriberi occurred.

Here then the conditions seemed to be in every way suitable for an inquiry into the part played by rice in the causation of beriberi. These labourers without exception still desired to return to a white rice diet and at this time the evidence of a connection between the consumption of white rice and beriberi was by no means convincing either to the general body of medical and scientific workers or to ourselves. The importance of reaching some conclusion regarding the origin of the disease cannot be over-estimated as the number of its victims in this Peninsula alone runs into many thousands annually. Throughout these States no labourers other than Tamils will consume parboiled rice unless compelled to do so and while there was any doubt as to the harmful influence of white rice no effective measures could be taken for the suppression of beriberi.

By acceding to the wishes of this group of labourers opportunity would be afforded for a thorough testing of the position of dietary factors as causative agents. The labourers were therefore given the option of returning to a white rice diet, after it had been fully explained to them that by so doing they ran the risk of contracting beriberi. Without exception they chose white rice but as for the purpose of comparison two parties were required, half the number only were allowed this diet. It was hoped also that by continuous observation of a large party of men on a parboiled rice diet, it might be determined whether, apart from its disagreeable musty odour, any grounds existed for the objections made to this rice.

At the time the investigation was commenced, April 1907, the 300 labourers then remaining were divided into two parties of approximately equal numbers, the one party at Kuala Ayer Baning, the other party at Durian Tipus. The clearings for the quarters had been made in virgin jungle and no case of beriberi had occurred at either place. The quarters were well raised from the ground, the floors were made of split bamboo, the walls of bark, and the roof of light attaps, thus they were well ventilated. In all cases the lines were well drained and near running water. The sanitary conditions were good.

In April all the labourers were examined and found to be free from any sign of existing or recent beriberi. The results of the physical examination of each person were recorded for future reference and an arrangement made that any person subsequently joining the parties should be carefully examined previously.

An interval was allowed to elapse during which any latent case might be expected to develop and, as all remained healthy, white rice was issued to the Durian Tipus party for the first time on May 12, the Kuala Ayer Baning party remaining on parboiled rice as before. The rices were of uniformly good quality and were obtained in quantities sufficient for one month at a time.

THE DIETS.

The daily ration was as follows:—

Rice	21·3 oz.	Coconut Oil ...	0·85 oz.
Dried Salt Fish ...	4·25 „	Coconut	1·50 „
Onions	1·75 „	Tea	0·12 „
Potatoes	1·75 „	Salt	0·1 „

The various articles composing this diet were submitted to analysis in this Institute by Mr. B. J. Eaton, and the percentage results obtained were as follows :—

White Rice—

Protein	Fat	Carbohydrate	Salts
7·45	0·17	78·02	0·51

Parboiled Rice—

Protein	Fat	Carbohydrate	Salts
7·8	0·53	76·92	0·72

Dried salt fish—

The species of fish so prepared are numerous, and the kind issued to the coolies varied to some extent. The average results from the analyses of a number of these species were—

Protein	Fat		Salts
35·7	2·96		13·24

Onions—

Protein	Fat	Carbohydrate	Salts
1·5	0·28	11·28	0·5

Potatoes—

Protein	Fat	Carbohydrate	Salts
1·8	0·2	31·66	1·04

Coconuts—

Protein	Fat	Carbohydrate	Salts
3·95	34·6	15·2	0·95

Based on these analyses the diet issued to those on white rice has been calculated to consist of—

Protein	Fat	Carbohydrate	Salts
91·451 grm.	43·708 grm.	499·165 grm.	23·064 grm.

and to contain—

Carbon	...	...	...	...	303·75 grm.
Nitrogen	...	...	...	...	14·8 „

The diet issued to those on parboiled rice has been calculated to consist of—

Protein	Fat	Carbohydrate	Salts
93·565 grm.	45·882 grm.	492·540 grm.	24·335 grm.

and to contain—

Carbon	...	...	...	...	302·34 grm.
Nitrogen	...	...	...	...	15 „

In accordance with European standards it is stated that 2 grm. of protein, 1·5 grm. of fat, 6 grm. of carbohydrate, and 0·5 grm. of salt per kilogram of body-weight are required. The average body-weight of the persons under observation was about 100 lb. and therefore the diet should contain—

Protein	Fat	Carbobydrate	Salts
90·72 grm.	68 grm.	272·16 grm.	20 grm.

and would contain—

Carbon	...	...	...	...	220·73 grm
Nitrogen	...	...	...	...	14·6 „

If now this calculated standard diet be compared with the diets consumed by the persons under observation, it will be seen that the issued diets can in no way be regarded as deficient. It is true that the amounts of fat are considerably less than in the standard diet but the deficiency in this respect is more than compensated for by the excess of carbohydrate.

Nearly half the protein in the diets issued is derived from rice, and it may be suggested that the treatment of the grain previous to milling renders the protein of parboiled rice more readily available than that of white rice. So far as a limited number of experiments have gone no evidence has been obtained in support of this suggestion.

It is well known that with a sufficiency of protein in any diet, fats and carbohydrates are to a considerable extent interchangeable and it must not be forgotten that the inhabitants of warm countries habitually consume relatively less fat and more carbohydrate than do the inhabitants of cold countries.

Histories of the Groups under Observation.

The parties were under constant medical supervision throughout the course of the inquiry and while the investigation was primarily directed to the part played by rice in the causation of beriberi, attention was also directed to other factors which have been suggested as bearing upon its etiology. Thus the incidence of ankylostomiasis, malaria, and dysentery, was ascertained and a general examination of all the coolies made at intervals of about a month and more frequent examinations of those showing signs of illness. In these examinations attention was particularly directed to the nervous system so that, in the event of beriberi developing, there should be a complete record of the patient's condition during the preceding months.

The parties as originally formed are designated Party No. I (Durian Tipus); Party No. II (Kuala Ayer Baning), and Party No. III, a small party at Pertang.

On July 1 the requirements of the road work necessitated the division of Party No. 1 into two groups. One group of approximately fifty (Party No. I A) remained at Durian Tipus, the other group, about one hundred in number (Party No. I B), were transferred to Juntai. The quarters at this latter place had been newly erected in a fresh clearing. The conditions as regards food remained unchanged. The individuals in these two groups being under similar dietary conditions were, for the purpose of this investigation, regarded as one party and were moved freely from one place to the other.

FIRST SERIES OF EXPERIMENTS.

PARTY No. 1 (May—June, 1907).

Party No. I comprised those individuals who were on white rice at Durian Tipus from May 12 until July 1, when the party was divided into two groups.

The history of Party No. I calls for no special comment. No case of beriberi occurred in it during the period May 12 to July 1.

PARTY No. 1 A (July—October, 1907).

This party was formed on July 1 of those of Party No. I who remained at Durian Tipus. The members of it had for the most part been on white rice since May 12, a few had joined after that date.

The first case of beriberi occurred at Durian Tipus on August 7, the second case on August 19, the third case on September 3, ten days after joining the party, and the fourth case on September 6. These dates indicate the time of commencement of an indisposition which terminated in or was followed by definite signs of beriberi: in nearly all cases this date is antecedent to the loss of the knee-jerk.

Discussion.

(*a*) Infection.

In view of the possibility of the disease being infectious in origin it is of importance to discuss fully the histories of the first cases. The first case had been from May 12 continuously in residence at Durian Tipus as had also the second. The third had been transferred from party No. I B (Juntai) on August 23, and the peculiar manner in which he came in contact with the first two cases of beriberi at Durian Tipus, to which reference will presently be made, suggested the likelihood of his having acquired the disease by infection. The fourth had also been intimately associated with the first two cases.

If an infection be assumed, the period of incubation from these cases may be fixed at ten to fifteen days. While there is nothing in the histories of the first two to suggest any intimate association, the third and fourth cases to develop were known to have been in intimate contact with the first two. The third case on his transfer to this party was inadvertently assigned quarters in the hospital, a partitioned off part of the quarters, and the fourth had been in this hospital under treatment for malaria since August 23.

As the first had been continuously in residence the question naturally arises as to how he acquired the infection. He is believed to have suffered from beriberi about two years previously in Java, but no residual paralysis or sign other than diminished knee-jerks remained to support this history. Still it might reasonably be suggested that he may either have had a relapse or have acquired an infection from outside.

As to the possibility that he may have acquired an infection from without, it is necessary to consider the conditions in this party for fifteen days preceding the development of the disease, that is from July 22 to August 7. On July 22 there were present in the party twenty-eight persons. During the interval under review three left the party and ten joined, five of these from Party No 1 B, at Juntai, four from Party No. II at Kuala Ayer Baning, and one from hospital at Kuala Klawang where he had been under treatment for pulmonary tuberculosis. Neither in Party No. I B nor in Party No. II did any cases of beriberi exist at this time.

There is no evidence that the man from hospital had beriberi previously and he had no signs of the disease on joining the party nor did he develop any

signs later. He died some months afterwards of pulmonary tuberculosis. There is little doubt that while in hospital this man was in contact with beriberi cases and the only remaining explanation is that this person may have been the means of conveying the hypothetical infection though he did not himself suffer from the disease, or only suffered from it in such mild form as to be impossible of recognition clinically.

Granting further that the deduction as to the period of incubation is erroneous and that this period is really longer, those who joined the party earlier than July 22 must be considered, excluding those joining from Parties No. I B and No. II which were known to be free from beriberi.

One joined the party from hospital on June 7. He developed no signs of beriberi.

A second joined the party from hospital on May 20 and after a stay at Durian Tipus subsequently joined Party No. II B at Juntai, returned to Durian Tipus on August 23 and developed beriberi there on September 3. If he acquired the infection in hospital the period of incubation would be fixed at some four months. In any case this man cannot be accused of having introduced the disease as he did not develop it until a month after the first case.

A third joined from hospital on May 20 and did not develop any signs of the disease.

A fourth joined from Pertang on July 5 and more than three months later developed beriberi. He had no signs of the disease when he joined.

A fifth joined from hospital on June 7 and after a stay at Durian Tipus joined Party No. I B at Juntai afterwards returning to Durian Tipus. He was sent to hospital on October 5 for treatment of an eye infection.

A sixth joined the party from gaol on June 20 and shortly afterwards was transferred to Party No. I B. He did not develop signs of beriberi.

Thus in a place in which it is known that no beriberi had occurred previously and in a person continuously in residence in that place for many months, during three months of which he was under special observation, the disease was developed. In seeking for an origin of the hypothetical infection in this place we must conclude that it was conveyed by some person from without who himself showed no signs. Any discussion as to its having originated *de novo* or that it was a relapse after two years' interval would be futile. The chances of infection having been introduced by persons not under observation, such as Malays or Chinese passing along the road, are very remote indeed.

(*b*) Diet.

Dealing now with the question of food as a source of the disease it will be noted that the members of Party No. I A were on white rice from May 12 until October 11. During this period thirty members of the party were on white rice for three months or longer, and amongst these, seven cases of beriberi occurred. During the time beriberi was present at Durian Tipus, August

7 to October 11, seven persons joined the party, either from Party No. II (Kuala Ayer Baning) or from hospital; there was no white rice issued at these places, and none of these seven developed beriberi, thongh they were exposed to the chances of an infection equally with the other members of the party. Of thirteen persons who came from Party No. I B where white rice was being issued, two subsequently contracted beriberi.

(*c*) Conclusions.

The results in this party therefore suggested the possibility that a diet of which white rice formed the staple was in some way concerned in the production of beriberi.

PARTY No. I B.

The first case of beriberi to develop in this party was taken ill on September 29. He had been in the party since its formation on July 1, and had been on white rice in all 141 days.

The second case developed on October 10. This man had been on white rice 152 days.

The third, fourth and fifth cases followed rapidly, the dates being October 12, 16 and 18. These cases had been on white rice 134, 158 and 160 days respectively.

Discussion.

(*a*) Infection.

From the view point of infection there is little to be said regarding this party. Such may easily have been introduced from Party No. I A at Durian Tipus, where the disease had broken out seven weeks previously. These two parties were only two miles apart and on holidays, which occurred twice a month, very slight restraint was placed upon their movements because, for the primary purpose of this inquiry, they were regarded as one party.

The introductions from outside into this party were one man who returned from Kuala Klawang hospital on July 12, and a second who joined Party No. I from Kuala Klawang gaol on June 22, and was transferred to Party No. I B on its formation, July 1. Five persons were transferred to this party from Party No. I A on July 23, after which date no other transfers were made. Six were moved from Party No. II to this party. None of these developed beriberi.

It is proper to mention here that in determining whether a given case was to be admitted as beriberi the most rigid exclusion was practised. Only cases presenting unequivocal signs of the disease were admitted. In every instance the diagnosis was based on the opinion of at least two medical men, in most instances by that of four. Where any doubt was cast upon the accuracy of the diagnosis the case was rejected. The result is therefore that, apart from the cases here recorded, there were many others which, in the opinion of the writers as well as of those associated with them in this inquiry, were really mild or obscure cases of the disease. The difficulties in

this respect will be appreciated by those who have had to deal with the disease clinically. No such doubtful case was at any time observed among the people on parboiled rice, and the inclusion of cases of this type occurring in the white rice parties does in no way strengthen the case for an infectious origin of the disease.

(*b*) DIET.

By October 11 seven cases had occurred in Party No. I A, and by October 18 five cases in Party No. I B. As there was apparently nothing further to be gained from a continuance of the white rice diet, it was thought that the time was suitable, by a change to parboiled rice, to observe the effect of this alteration of diet upon the course of the outbreak. Accordingly parboiled rice was substituted for white rice in the diet of Party No. I A on October 12, and in that of Party No. I B on October 19.

After this change no case of beriberi occurred in either party and such cases as showed signs suspicious of beriberi rapidly got well.

(*c*) CONCLUSION.

This abrupt cessation of the outbreak constitutes important evidence of a causative relationship between the consumption of white rice and beriberi. It is known, however, that diseases of infectious origin do tend to die out abruptly and this cessation is not incompatible with an hypothesis of an infectious origin for the disease. It is possible that the cessation of the outbreak on the change of rice was merely a coincidence or that all the susceptible individuals had developed beriberi.

Party No. II (May—October, 1907).

This party located at Kuala Ayer Baning was employed for purposes of comparison with the results in Parties No. I A and No. I B. At this place only parboiled rice had been issued since the quarters were first occupied in September, 1906. These conditions were continued till October, 1907, and the party was under detailed observation from May till October. The same care was taken in examining the coolies comprising this party as was taken in dealing with members of the white rice party.

DISCUSSION.

At one time or another 143 persons were members of this party. Of these 112 were on parboiled rice continuously from May 1 until the date (August 7) when beriberi first appeared in Party No. I A, and 89 remained on parboiled rice until the change to white rice on October 19. There were present in the party for at least three months 121, and there were present during the period August 7—October 19, 131.

During the period May 1—October 19, men left the party to go to hospital and some two or three were sent to gaol. The majority of these returned to the party on their recovery or release. Of such returns there were in all twenty-

five, twenty-one from hospital and four from gaol, who may be regarded as potential sources or carriers of an infection in contrast to thirteen who joined Parties No. I A and No. I B during the same period. In addition, this party was nearer a settlement than either Party No. I A or Party No. I B. It thus appears that the chances for the introduction of a hypothetical infection were much greater in the control Party No. II than in Parties No. I A and No. I B. Despite this preponderance of factors favouring the introduction of infection, no case of beriberi appeared in this group.

Summary of Results in the First Series of Experiments.

The results in Parties No. I A and No. I B on white rice may be tabulated as follows:—

(*a*) Assuming an infectious origin for beriberi.

Party No. I A.

Case	I	August 6.
,,	II	,, 19.
,,	III	September 3 (exposed to infection August 23).
,,	IV	,, 6 (directly exposed to infection August 23).
,,	V	,, 18.
,,	VI	October 5 (transferred from Party No. I B October 1).
,,	VII	,, 10.

Party No I B.

Case	I	September 29.
,,	II	October 10.
,,	III	,, 12.
,,	IV	,, 16.
,,	V	,, 18.

(*b*) Assuming a dietary origin.

	Up to	30	days	on white rice,	cases	...	0
From	31 ,,	60	,,	,,	,,	...	0
,,	61 ,,	90	,,	,,	,,	...	1
,,	91 ,,	120	,,	,,	,,	...	4
,,	121 ,,	150	,,	,,	,,	...	3
,,	151 ,,	160	,,	,,	,,	...	4

In Party No. II, a control group on parboiled rice, no case of beriberi occurred.

SECOND SERIES OF EXPERIMENTS.

Party No. II (October, 1907—May, 1908).

In view of the results obtained in the first series of experiments it was decided to reverse the conditions and to place this party, hitherto on parboiled rice, on white rice, and to place Parties No. I A and No. I B henceforward on

parboiled rice. This change was made in Party No. II on October 19, no other alteration, dietetic or otherwise, being made.

The better to safeguard this party from infection it was decided that so far as it was possible to do so, no one should be allowed to join the party from outside. All persons sent to hospital were on their return assigned to other parties. In consequence of this procedure the numbers of the party materially diminished during the course of the investigation and gradually it came to be a more or less selected party, only the more robust of its members remaining.

On October 19, 1907, there were at Kuala Ayer Baning 111 people, a number of whom left or were transferred soon after that date. The removal of the party from Kuala Ayer Baning took place on March 22; they were, therefore, under observation at that place for 165 days. Fifty-eight of the party had been continuously present since October 19 and one from October 28. Five men joined the party from hospital on October 2 and one joined on October 28. One other joined from hospital on November 13. Thenceforward no one was allowed to join this party.

This period of 165 days at Kuala Ayer Baning considerably exceeded the minimum interval which elapsed at either Juntai or Durian Tipus between the first issue of white rice and the outbreak of beriberi. Seventy-seven coolies were under observation for at least ninety days.

As the work of road construction had been completed at Kuala Ayer Baning by March 22, the labourers, fifty-four in number, comprising the party on that date were transferred to new quarters at the 64th mile. These quarters had been erected about two months previously and had not been occupied. Between the old and new quarters the party was not exposed to any possible infection so far as is known.

On April 9 one man developed beriberi and about the same time a second developed the disease. Owing to the requirements of the work it was found necessary on April 23 to transfer the remaining members of the party to quarters at the 61½ mile. These quarters had been occupied since November 18 by Party No. I, which comprised 90 to 110 persons among whom no case of beriberi had occurred since the change of rice on October 11 and 19. The two cases of beriberi which had occured at the 64th mile were, as soon as the diagnosis was established, transferred to the quarters at 61½ mile in order to be more directly under medical care. As the remainder of the party were transferred soon afterwards it is clear that abundant opportunity was afforded by this movement for the transference of an infection if such had existed.

When the change had been effected there were in occupation of the quarters at the 61½ mile 131 people, forty-two who had been and were now continued on white rice, eighty-five who had been and were now continued on parboiled rice, and four who had been transferred from the 64th mile previous to April 23. Two of these latter were cases of beriberi and two were suspected cases.

The food for the mixed party, other than the rice, was prepared in a common kitchen; the rices were prepared in separate kitchens and, in order to be quite

certain that the people on white rice were not given parboiled rice or *vice versa*, the food was issued to the parties at different hours. In all other respects the parties were under identical conditions.

On April 25 one man developed beriberi. On May 1 a second developed the disease and three others on May 10 and May 11.

On May 12 all the people remaining on white rice at the 61½ mile were changed to parboiled rice. After this date no case of beriberi occurred.

In the parboiled rice group at the same place, although carefully observed for possible cases of beriberi, no signs were noted.

Discussion.

(*a*) Infection.

If the disease is an infectious one it is difficult to explain the course of events at this place since in the one group of thirty-five persons to whom white rice was being issued, there occurred five cases of beriberi, while in the other group of eighty-five persons, to whom parboiled rice was being issued, no sign of the disease appeared. The members of the two groups occupied the same quarters, freely intermingled with one another and were, as far as could be known, under identical conditions in all respects save only in the matter of diet.

As regards the question of place infection the transfer of the party had no effect on the progress of the outbreak and to further test the possibility of the old quarters being an infected place some thirty persons who had been on parboiled rice at Durian Tipus since October 12 and in whom no case of beriberi had occurred since that date, were removed to these quarters on May 7. These remained in the 64th mile quarters for one month, a period exceeding by a fortnight, the duration of residence of the white rice party in these quarters before the first case of beriberi occurred. Save for the change of place the conditions, dietary, &c., remained unchanged and no sign of beriberi was observed among them.

As possibly further bearing upon the question of infection by one of the suggested modes, namely, through fæcal contamination, it may be noted that during the time the two parties were together at the 61½ mile an outbreak of amœbic dysentery occurred. This disease showed no selective action on the parties but attacked members of both, eight cases occurring in the parboiled rice party and six cases in the white rice party.

(*b*) Diet.

From October 19 to March 22 this party was housed at Kuala Ayer Baning and on white rice. The history of the outbreaks of beriberi at Durian Tipus and Juntai had led us to believe that if the consumption of white rice were responsible for the disease, an average period of about 125 days was required. This party was on white rice for 156 days and no sign of the disease had appeared. It is to be remembered, however, from the view point of the dietary hypothesis, that owing to the conditions which had

been laid down the party became eventually one composed of selected individuals who may be presumed to have been more resistant to the possible harmful influence of white rice.

On March 23 the party was transferred to new quarters at the 64th mile, and on April 7 the first case of beriberi occurred. When two definite cases had developed, the party was transferred to the 61½ mile and formed part of a large party at that place. Cases of beriberi continued to appear in this group until the change to parboiled rice on May 12.

Change of place had therefore no effect upon the progress of the outbreak and no evidence was forthcoming that members of this group were able to convey the disease to persons on a parboiled rice diet.

(*c*) Conclusion.

These results indicate that place *per se* or considered as a nidus of infection has no influence upon the development of beriberi, and confirmed our belief that the disease is not a communicable one, but has its origin in diet.

PARTY No. I (October, 1907—May, 1908).

This party, now composed of Parties No. I A and No. I B subsequent to the change to parboiled rice, was employed for comparison with the results in Party No. II. In Party No. I A this change dates from October 12, and in Party No. I B from October 19. The party continued on parboiled rice until the end of the investigation in June, 1908. One group remained at Durian Tipus until transferred to the 64th mile on May 7; the other group, formerly at Juntai, was transferred to the 61½ mile on November 18. No case of beriberi occurred in either group after the change to parboiled rice.

Discussion.

(*a*) Infection.

On October 19, all the cases of beriberi, eight in number, were at the Durian Tipus quarters. They remained in this place until November 3, when seven of them were sent to hospital at Kuala Klawang: one, being then too ill to be moved, remained. Attention is called to this fact as bearing still further upon the question of infection including the influence of place. In these quarters seven cases of beriberi had developed in eight weeks among an average population of about thirty. There were now eight cases of beriberi in different stages in the quarters, an undoubted focus of infection if the disease were a communicable one, yet no further sign of the disease showed itself.

It may be that all susceptible persons in this party had by this time become affected, and that this may explain the cessation of the outbreak coincident with the change in diet. Against this stands the fact that on November 1, fourteen labourers, who had just arrived from Java, joined this party while the beriberi patients were still at Durian Tipus, and on November 15, twenty-two

more such persons joined the party. It might have been expected that among these there would have been some who were susceptible.

One man who had developed the disease at Pertang (Party III) on December 28 was transferred to this party on January 5, in order to be near medical care. Cases of beriberi were also transferred to this party from Party No. II, and cases of beriberi continued to develop in Party No. II while occupying the same quarters as Party No. I. No attempt was made to isolate such cases, in this respect following the universal custom in the treatment of beriberi. It resulted in consequence that cases of beriberi, in all stages of development, were in contact with healthy people, yet at no time was there any evidence that the disease could be communicated to a person on parboiled rice.

The party under review was a large one, 202 individuals were present in it at one time or another from October, 1907, to May, 1908; 156 of these were present for not less than three months continuously, and 108 for not less than six months continuously.

During this period twenty-five persons returned from hospital, and twenty-one joined the party from Party No. III Pertang. From time to time also some joined from Party No. II.

(*b*) Conclusion.

It will be seen that in this large party there was abundant opportunity for the introduction of an infection, yet no sign suggestive of beriberi was observed in any of its members.

PARTY No. III.

This was a small party of men in the employ of the same contractor, and engaged on his rubber estate at the village of Pertang. Only parboiled rice had been issued to the labourers on this estate from August 2, 1906, and there had been no cases of beriberi. From August 16, 1907, white rice was issued, and continued till May 31, 1908. The party was under observation from August 1, 1907. The number remaining there continuously during this period was eight. The number on white rice continuously for at least three months was thirty-six, and for at least six months twelve.

One case of beriberi only occurred at this place on December 28, 1907. He was transferred to Party No. I on January 5, 1908.

Discussion.

From the point of view of infection in Party No. III, the patient remained among them for seven days after he had developed the disease. Between December 28, 1907, and January 5, 1908, there were in all thirty people in this party. In addition, it should be stated that this party was much less isolated than the other parties under observation.

As regards food their proximity to a village rendered it easy for the men to obtain food other than that supplied to them.

The white rice issued at this place was from the same stock as supplied to Parties No. I and No. II.

No special importance is attached to the results in this party, as owing to its situation, there were many uncontrolled factors in operation.

Summary of Results in Second Series of Experiments.

Into a large party on parboiled rice cases of beriberi, which had developed on white rice diet, were introduced. There was no conveyance of the disease to persons on parboiled rice.

Place *per se* or considered as a nidus of infection has no influence on the development of beriberi.

In a mixed party cases of beriberi occurred only among persons on white rice. An outbreak of dysentery affected both groups alike.

Diseases other than Beriberi in the Groups under Experiment.

(*a*) Helminth Infections.

In view of the suggestion that has been made attributing to the presence of nematode worms in the intestine, particularly ankylostomes, a causative action in the production of beriberi, examinations were made to determine what proportion of the coolies under observation harboured these parasites. The individuals were not selected in any way so that the results below probably indicate with fair accuracy the incidence of the various intestinal parasites.

Party No. 1.

No ova found	26	times
Ova ankylostomes only	19	,,
Ova ankylostomes and ascaris	6	,,
Ova ankylostomes and trichocephalus	6	,,
Ova ankylostomes ascaris and trichocephalus ...	10	,,
Ova ankylostomes and larvæ *Strongyloides stercoralis*	1	,,
Ova ankylostomes, trichocephalus and larvæ *Strongyloides stercoralis*	1	,,
Ova ascaris only	7	,,
Ova ascaris and trichocephalus	3	,,
Ova trichocephalus only	3	,,
Total number of examinations ...	82	
Percentage harbouring ankylostomes ...	52·4 %	

PARTY No. II.

No ova found	5	times.
Ova ankylostomes only	18	„
Ova ankylostomes and ascaris	13	„
Ova ankylostomes and trichocephalus	5	„
Ova ankylostomes, ascaris and trichocephalus ...	8	„
Ova ascaris only	2	„
Ova trichocephalus only	3	„
Ova ascaris and trichocephalus	4	„
Total number of examinations ...	58	
Percentage harbouring ankylostomes	75·8	per cent.
Percentage of all examinations in which ankylostome ova were found	62·1	„

Examination of fæces of individuals who afterwards suffered from beriberi.

No ova	6	times.
Ova ankylostomes only	4	„
Ova ankylostomes and ascaris	3	„
Ova ankylostomes and trichocephalus	2	„
Ova ankylostomes, ascaris and trichocephalus ...	2	„
Ova ankylostomes and larvæ *Strongyloides stercoralis*	1	„
Ova ascaris and trichocephalus	1	„
Total number of examinations ...	19	
Percentage of individuals who suffered from beriberi harbouring ankylostomes... ...	63·2	per cent.

The percentage of persons harbouring ankylostomes among those who suffered from beriberi was therefore practically the same as the percentage among the whole population under observation. The number of examinations is admittedly too small to be conclusive on the point, but the results indicate that ankylostomes play no part in the causation of beriberi.

(*b*) BLOOD PARASITES.

Upwards of a thousand of these examinations were made and systematic observations on the blood of the beriberi patients failed to reveal, by the staining methods employed, the presence of any organism likely to have a causal relationship to the disease.

During the period of slight pyrexia which commonly preceded the onset of definite signs of beriberi, malaria parasites were found in the blood on several occasions. In such cases it may be said that the attack of malaria precipitated the onset of beriberi or *vice versa*.

An attempt was made, by taking blood films from a number of persons, to obtain a series of films extending over some months preceding the onset of beriberi in a given individual. The choice of individuals was not fortunate, however, and the most that was obtained was that in one case the series extended over a week preceding the onset of beriberi. In this case no parasites were found.

GENERAL RESULTS AND CONCLUSIONS.

(1) In the course of a systematic inquiry specially undertaken to test the position of white rice as a causative agent in beriberi it was observed that twenty cases of this disease occurred among 220 people on white rice who were continuously present in the various parties during the course of the outbreaks. In the control parties on parboiled rice during the same periods and under similar conditions, among 273 people no sign of the disease appeared.

(2) Since all cases presenting equivocal signs of the disease were excluded we are of opinion that there were many other cases which in the ordinary routine of clinical practice would have been regarded as beriberi. Such cases only occurred among people who consumed white rice, and their inclusion would not strengthen the case for an infectious origin of the disease.

(3) No case of beriberi occurred in any person who had been on white rice less than eighty-seven days.

(4) Systematic examinations were made of the blood and urine of patients suffering from beriberi. Various methods of examination were employed, but in no instance were any organisms found except those well known as the causative agents of other diseases.

(5) In the course of the inquiry patients in various stages of beriberi were at times in contact with parties of men on parboiled rice. The results of observations made on such occasions furnished evidence that the disease is not a directly communicable one.

(6) Removal of patients suffering from beriberi from one place to another did not influence the progress of the disease and removal of entire parties from the place where the disease had occurred did not influence the progress of the outbreak so long as they continued on white rice. These experiments suggest although they do not prove that place *per se* or considered as a nidus of infection has no influence upon the development of beriberi.

(7) In three instances in which definite outbreaks of beriberi occurred among parties on white rice, substitution of parboiled rice was followed by cessation of the outbreak.

(8) The outbreaks of beriberi cannot be attributed to deficiency in the diet issued in respect of protein, fat, carbohydrate or salts.

(9) No evidence was obtained to show that any article of food other than white rice was a possible source of a causative agent of the disease.

(10) Ankylostomes and other nematode worms were not found in a larger

proportion of patients suffering from beriberi than in the general population under observation.

(11) The general results lend support to the view that the disease beriberi as it occurs in this Peninsula has, if not its origin in, at least an intimate relation with white rice, and justify further research along these lines.

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The Etiology of Beriberi.

The suggestion of a causal relationship between the consumption of white rice and the disease beriberi was first formally made in this country by Braddon [1]. This observer also drew attention to the important fact that those who consumed rice which had been parboiled before husking remained free from the disease, as did also the native Malays who consumed rice prepared by primitive methods of pounding and winnowing.

A series of observations made by the writers [2] in 1907 on two parties of labourers, under conditions which excluded or adequately controlled the operation of factors other than diet, confirmed the correctness of this view of the causation of the disease. The prior observations of Fletcher [3] and Lucy [4] in this country, and of Dubruel [5] in Indo-China, and the recently published observations of Ellis [6] furnish further testimony, and it may now be claimed that the theory rests on a solid basis of evidence.

The mechanism by which white rice was able to produce this result has remained obscure.

Braddon suggested that "the cause of the disorder is not indeed rice, *qua* rice, or as an article of diet, but diseased rice; rice with which poison derived from decay, due perhaps to some fungus or mould, or germ, or spore, originally perhaps growing upon the husk, has become mixed during the process of milling; or upon which such fungus may have grown and such poison have been produced after decortication." Eijkman [7] from experiments on fowls concluded that a definite poison exists commonly in rice and that for this poison or its effects something in the pericarp is an antidote. Dubruel believed in the ingestion of an organism associated with white rice, which organism multiplying in the body produced the disease.

Following the line of thought suggested by the poison hypothesis, researches were undertaken to determine whether, from white rices actually associated with outbreaks of beriberi, there could be extracted by means of various solvents any substance or substances recognizable by chemical methods as poisonous in character. These researches failed in their object, though it is admitted that the accuracy of the poison hypothesis was not thereby disproved.

Certain results which emerged from chemical analysis and histological examination of the rices turned attention to the possibility of an explanation of the course of events on an hypothesis of a defect of nutrition. That this explanation was inadequate, if dietary constituents as estimated by the ordinary analytical methods were alone considered, had been shown in the preliminary investigation.

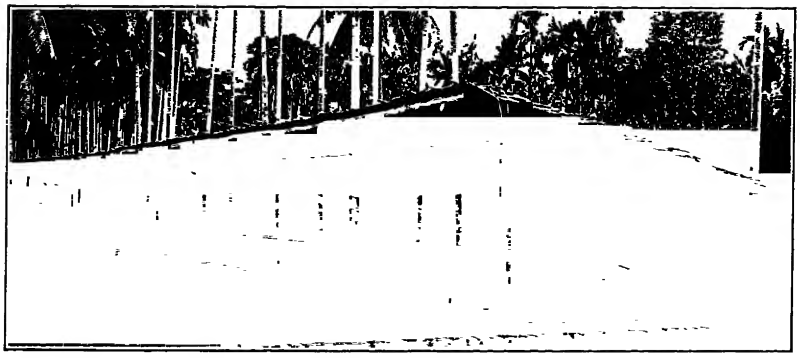

FIG. 1.—FOWL RUN, SHOWING ARRANGEMENT OF CAGES.

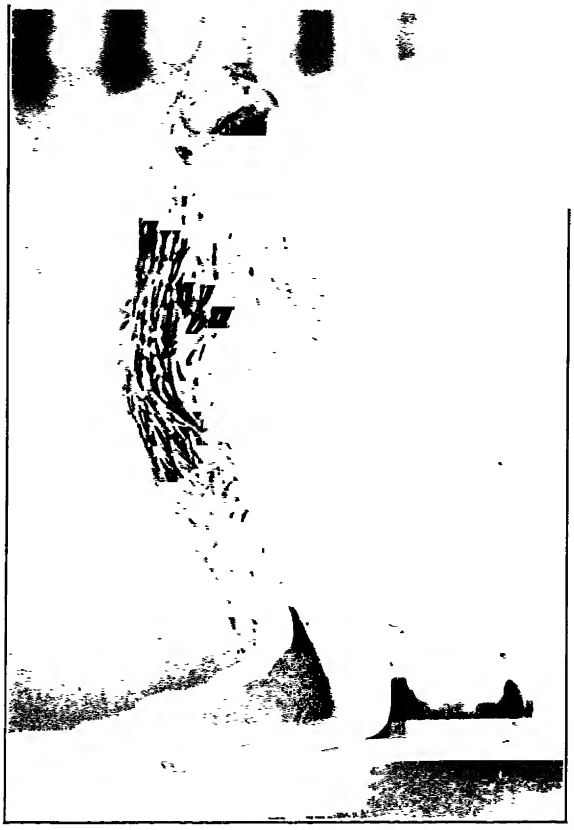

FIG. 2.—FOWL FED ON WHITE RICE.
Early Stage of Polyneuritis.

By a series of experiments on domestic fowls, the details of which will be supplied in a later publication, it was shown that these animals when fed on various kinds of rice were sensitive to differences between them. The fowls were confined in separate compartments and were in all respects under identical conditions. The manner of arrangement of the cages is shown in Plate I, fig. 1.

By further and repeated experiments with rices known to have been associated with outbreaks of beriberi, and with controls under identical conditions fed on parboiled rice, it was established that a certain reaction in fowls might be taken as an indicator of the beriberi-producing power of a given rice when forming the staple of the diet in man. Whether the disease produced in fowls be accepted or not as analogous to beriberi in man, the validity of the arguments here advanced remains unimpaired.

Rices were available that were known to have been associated with outbreaks of beriberi, samples having been taken daily during the continuance of the preliminary inquiry in 1907; also through the courtesy of Dr. J. D. Gimlette and Dr. G. D. Freer we were enabled to procure white rice which was being consumed prior to an outbreak of beriberi among Malays at the Kuala Lumpur police depot, which outbreak ceased on changing the rice supplied to the parboiled variety. It was shown that these rices when fed to fowls constantly produced a certain disease in a large proportion of them, while parboiled rice as constantly failed to produce this result in groups under identical conditions. This disease is characterized by paralysis of the legs (Plate I, fig. 2, and Plate II, fig. 3), followed by paralysis of the wings (Plate II, fig. 4) in the more severe cases. In cases showing a moderate degree of paralysis the gait resembles very closely that seen in beriberi. The nerves of fowls suffering from this disease show typical Wallerian degeneration (Plate III, fig. 5).

It is our belief that this disease, *polyneuritis gallinarum*, is truly analogous to beriberi in man, similar in its etiology, in its clinical manifestations, and we have shown them to be identical in their pathological effects, and that its occurrence should be held as important confirmatory testimony of the connection between white rice and beriberi. It is desirable, however, to emphasize the point that the acceptance or nonacceptance of this opinion is immaterial to the argument; for this purpose the occurrence of the disease is employed only as a reaction. The fact that certain white rices when forming the staple of a diet in man produce beriberi rests on quite other testimony than that supplied by experiments on domestic fowls.

The commercial varieties of white rice are numerous, but in this country, apart from the grading as to quality, two are in common use and are known, respectively, as Siam and Rangoon.

From epidemiological considerations and from experimental evidence it appears that Siam rice is considerably more potent in its beriberi-producing powers than Rangoon rice.

The proteins, fats, carbohydrates, and ash were determined for the different varieties of rice which had been employed in the experiments, with the following percentage results calculated on dried material.

	Proteins	Fats	Carbohydrates	Ash
White rice (Siam)	9·07	0·17	90·11	0·65
,, (Rangoon) ..	8·44	0·81	89·90	0·85
Parboiled rice	9·48	0·51	89·12	0·89

A comparison of these results shows that the only marked difference among the rices was in respect to fat, which was most abundant in the variety known as Rangoon, less abundant in parboiled rice, and still less abundant in Siam rice. These observations, taken in conjunction with the experimental results in fowls, excluded the possibility of an explanation of the origin of beriberi on the ground of a deficiency in fat. It will be noted that these analyses did not include an estimation of the relative proportions of the inorganic salts composing the ash, nor did they take account of the manner of combination, organic or inorganic, in which these substances originally existed in the rice grain.

By a method devised in this laboratory, sections of the various rice grains were obtained of sufficient thinness to permit the examination in detail of their histological characters. By suitable staining methods it was shown that in parboiled rice (Plate III, fig. 7) remnants of the pericarp remained attached to the rice grain, whereas in Siam rice (Plate III, fig. 8) the pericarp and the layers subjacent to it (subpericarpal layers) had been polished away. It would appear that parboiling renders the grain tough and nonfriable, in consequence the subpericarpal layers cannot be removed so readily as in the untreated grain. It was further demonstrated that the layers so retained in parboiled rice contained the most of the aleurone and oily material present in rice grains. Rice as prepared by primitive methods (Malay rice) was similarly examined, and, as might have been expected from the pounding to which this rice had been subjected, parts of the subpericarpal layers were chipped off to a varying extent, but on the whole these layers were retained to a greater extent than is the case with white rice.

Early in the course of the experiments the observation was made that parboiled rice subjected to exhaustion with hot alcohol and thereafter carefully dried in the sun to free it from alcohol, produced when fed to fowls a disease indistinguishable from that observed in birds fed on white rice, although such parboiled rice in its original state was incapable of producing this result, however long continued.

The association of the observations referred to in the two preceding paragraphs seemed to point a way to a solution of the problem. It had been shown that white rice as prepared in the mills of this country produced the same results in fowls as white rice known to have been associated with beriberi. If, now, a substance or substances residing in the outer layers which are polished away in white rice and are retained in parboiled rice could be added to white rice and so prevent its harmful effects it was conceived that the nutritive hypothesis would thereby be supported.

FIG. 3.—FOWL FED ON WHITE RICE.
Polyneuritis.

FIG. 4.—FOWL FED ON WHITE RICE.
Late stage of polyneuritis.

In accordance with this idea the following experiments were initiated :—

A rice mill in Singapore was visited and there was obtained (*a*) a quantity of the grain deprived of the husk; (*b*) a quantity of the polished rice from the same lot of grain, that is, the grain from which the subpericarpal layers had been polished off; (*c*) a quantity of the polishings, that is the material removed subsequent to the separation of the husk and which includes the pericarp with the subpericarpal layers. The miller estimates that forty parts of paddy produce twenty-five parts of white rice, five parts of polishings and ten parts of husk The polishings are sold as food for cattle and the husks are burned as fuel in the mill.

Experiment A.—Twelve fowls were fed on the husked grain for five weeks.

Result: All remained healthy.

Experiment B.—Twelve fowls were fed on the white rice alone.

Result: In five weeks six had developed polyneuritis; two were dead, one having suffered from polyneuritis and one from a disease other than polyneuritis; five fowls remained healthy.

Experiment C.—Twelve fowls were fed on rice taken daily from the same bag as that used in experiment B; in addition, polishings in the form of emulsion, in amount equal to that milled from the quantity of rice consumed, were fed daily by a tube passed into the crop. This quantity was subsequently diminished week by week until only 3 grm. of polishings per kilo of body weight were being given daily. This amount sufficed to maintain the fowls in health and in constant weight.

Result: The experiment was continued for seven weeks and all remained healthy.

The result was subsequently confirmed for rice taken from places where known outbreaks of beriberi had occurred.

It will be understood that these three experiments were in progress simultaneously and that the fowls were in all respects under identical conditions.

Experiment D.—Part of the original paddy was taken and milled by a Malay woman by primitive methods into the finished product as eaten by Malays. Eight fowls, fed for five weeks on the rice prepared from the original paddy by the Malay method, remained healthy. Eight fowls only were used for this experiment, as the quantity of paddy then remaining sufficed only for this number for the time it was estimated the experiment would last.

Attention is drawn to the important point that the products used in these experiments were all derived from the same lot of paddy, and the results force us to the conclusion that it is the polishing process which is essentially at fault; the polishing of white rice removes from the seed some substance or substances essential for the maintenance of the normal metabolism of nerve tissues.

To elucidate the point as to whether rice when freshly milled is less harmful than that which has become stale, an assistant was stationed in Singapore who sent daily to the laboratory by the most expeditious route a quantity of rice milled on the day of dispatch. Twelve fowls were fed on this rice and five developed polyneuritis in four weeks. This result, which is similar to that obtained in other experiments, when fowls were fed on rices milled from four weeks to two years previously, disposes of the suggestion that the harmfulness of white rice is due to it staleness or the development in it of a poisonous substance or substances subsequently to its being milled. The root of the evil lies in the milling process itself. The result further indicates the inadequacy of preventive measures founded on the poison hypothesis in regard to the use of freshly milled rice.

An experiment was now planned to determine whether a parboiled rice proved harmless, could by exhaustion with hot alcohol be reduced to such a condition that it would produce polyneuritis when fed to fowls, and whether the substances so extracted when fed to fowls with a white rice proved harmful could prevent the development of polyneuritis. For this purpose parboiled rice was repeatedly exhausted with hot alcohol. The alcoholic extracts were concentrated *in vacuo* at a temperature of 52° C., freed from alcohol and the residue emulsified in distilled water. Experiments with these products showed that fowls fed on the exhausted, parboiled rice contracted polyneuritis, and that birds fed on a white rice, proved harmful by previous experiment, remained healthy if they received in addition a quantity of the extract.

Having by these and other experiments, the details of which are omitted so as not to encumber the argument, arrived at the point where it was clear that the essential cause of beriberi was to be sought for in a nutritive defect, further efforts were made to determine by chemical methods precise differences between various rices. Such differences, if they are to furnish an adequate explanation for the origin of beriberi, must be in accordance with clinical observations and the experimental results in fowls.

In view of the important rôle played by phosphorus compounds in the metabolism of nerve tissues, the amount of phosphorus in various kinds of rice was determined as phosphorus pentoxide. The result of a large series of observations showed that a reduction in the amount of phosphorus pentoxide obtained from rice was directly related to the probability of the rice producing beriberi; in other words, the higher the phosphorus content of a rice the less was the liability of that rice to produce the disease, and *vice versa*.

Thus, a sample of parboiled rice which was fed to fowls over many weeks all remaining healthy, was found to contain 0·469 per cent. P_2O_5; and a sample of white rice which produced polyneuritis in fowls yielded 0·277 per cent. P_2O_5. The rice polishings employed in experiment *C* yielded 4·2 per cent. P_2O_5.

From a series of observations it was determined that a fowl under the conditions of our experiments, weighing from 1,200 to 1,400 grm., required 60 grm. of parboiled rice daily to maintain it in health and in nutritive equilibrium. In experiment *C* it was determined experimentally, the chemical analysis being then unknown, that when fed on white rice a fowl of this weight required the addition of about 3·5 grm. of polishings to preserve it in nutritive equilibrium. From the data given above it may readily be calculated what amount of polishings added to white rice is required to raise the phosphorus content of the white rice diet to that of the parboiled rice. Thus:—

	Grm. P_2O_5
60 grm. of parboiled rice	0·3120
60 grm. of white rice	0·1662
Difference	0·1458

Polishings contain 4·2 per cent. of phosphorus pentoxide.

Calculated from the phosphorus content, therefore, 3·47 grm. of polishings added to the 60 grm. of white rice supplied to a fowl of 1200 to 1400 grm. weight should preserve it in

FIG. 5.—TEASED PREPARATION OF SCIATIC NERVE OF FOWL SUFFERING FROM POLYNEURITIS. WALLERIAN DEGENERATION.

FIG. 6.—CROSS SECTION OF RICE GRAIN, AFTER REMOVAL OF THE PALLÆ OR HUSKS, SHOWING THE PERICARP AND SUBPERICARPAL LAYERS INTACT.

FIG. 7.—CROSS SECTION OF RICE GRAIN TREATED BY PARBOILING BEFORE MILLING, SHOWING THE SUBPERICARPAL LAYERS INTACT.

FIG. 8.—CROSS SECTION OF GRAIN OF WHITE RICE (SIAMESE). SUBPERICARPAL LAYERS HAVE BEEN REMOVED IN POLISHING.

nutritive equilibrium. From experimental observation 3·5 grm. of polishings had been shown to accomplish this result. This can scarcely be regarded merely as a coincidence, but its exact significance and importance cannot yet be estimated.

Fowls receiving nothing but water do not develop polyneuritis, while fowls receiving only polished rice and water do. No satisfactory explanation of this observation has as yet been obtained, but further researches are in progress. Meanwhile the amount of phosphorus estimated as phosphorus pentoxide contained in a given rice may be used merely as an indicator of its liability or otherwise to produce beriberi.

We are greatly indebted to Mr. B. J. Eaton, chemist in this Institute, for valuable assistance in the chemical part of this investigation, and to Dr. R. D. Keith for suggestions as to methods for the examination of the nerves.

SUMMARY.

(1) Beriberi is a disorder of metabolism and, as it occurs in this country, is associated with a diet in which white rice is the principal constituent.

(2) White rice as produced in the mills here commonly makes default in respect of some substance or substances essential for the maintenance of the normal metabolism of nerve tissues. These substances exist in adequate amount in the original grain and in superabundant amount in the polishings from white rice.

(3) The estimation in terms of phosphorus pentoxide of the total phosphorus present in a given rice may be used as an indicator of the beriberi-producing power of such rice when forming the staple of a diet in man.

The prevention of beriberi in this country will be achieved by substituting for the ordinary white rice a rice in which the polishing process has been omitted, or carried out to a minimal extent, or by the addition to a white-rice diet of articles rich in those substances in which such white rice now makes default. One such article which is cheap and readily obtained is the polishings from white rice.

The use of parboiled rice as suggested by Dr. Braddon will achieve a like result, provided that the polishing process is not carried beyond the limited extent now customary.

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The Philippine Journal of Science, Vol. v, No. 1, February, 1910.

Discussion on Beriberi at the First Congress of the Far Eastern Association of Tropical Medicine.

With reference to the observations on the nutritive value of the diets, I do not think that we can estimate these from the composition of the various foodstuffs recorded in textbooks because, in our experience, these records show considerable differences from the results of analyses carried out by us.

There are numerous species and varieties of rice; these differ in composition. Beef in the Tropics is poorer in fat and pork is richer in fat than the corresponding articles as generally met with in Europe. If, then, we are to derive any information from the composition of the diets in respect to proteins, fats, carbohydrates and salts, actual analyses of the foodstuffs as issued must be made.

In our work at Durian Tipus we analysed all the foodstuffs issued, and, on comparing the diet issued to the party on parboiled rice with that issued to the party on white rice, no really important differences were observed and both diets, considered in this way, should have sufficed for the physiological requirements of the individual.

We believe in our work at Durian Tipus that we excluded the operation of every other factor save rice in the production of beriberi.

Comparison of the composition of parboiled and white rices showed differences in respect to fat and ash, but the difference in amount of fats could not account for the results if we consider these bodies merely as the esters of fatty acids. The difference in amount of ash we have shown to depend mainly on the phosphorus compounds. Further investigation is necessary to explain the significance of this.

I believe that the method of estimating diets from the amount of proteins, fats, carbohydrates and ash contained in them will require reconsideration, and in all probability readjustment. In the light of recent research this method has shown itself to be crude and incapable of showing differences which may be of vital importance to the physiological requirements of the individual.

Doctor Aron's researches are of the greatest importance, and shed a large amount of light on this difficult problem, but I doubt if the difference in respect of phytin will explain the results.

In the case of the parboiled and white rices used by us and both derived from the same kind of paddy, we have estimated the phosphorus pentoxide in the washed and dried rices, because the rices are washed previous to cooking.

Now, if we consider all the phosphorus estimated in this way to be com-

bined as phytin, and that a man receives one and a third pounds of rice daily, we find that the men on white rice would receive about 1·5 grammes of phytin daily, and those on parboiled rice about 3 grammes of this substance.

The matter is, however, one of scientific interest, and at present of no practical importance to those engaged in the prevention of beriberi.

Our researches have conclusively shown that beriberi can be prevented by the use of unpolished rice, and as surely produced by the use of highly polished rice.

We have furnished you with three methods by which it is possible to determine the liability or otherwise of a given rice to produce beriberi.

(1) Chemical.

(2) Histological.

(3) By feeding experiments on fowls.

Of course, if the dietary of those peoples among whom beriberi is occurring be improved, the use of highly polished rice might be continued and no untoward effect occur, but so long as these peoples continue to partake of a diet in which rice constitutes the staple, our efforts must be directed to maintaining the rice at a standard sufficient for their physiological requirements.

I wish to correct here one misapprehension. It is not the removal of the pericarp which makes the rice harmful, but of the layers subjacent to the pericarp (subpericarpal layers); the cells composing those layers differ in respect of their constituents from the cells composing the central part of the endosperm.

The Lancet, December 17, 1910.

The Etiology of Beriberi.

In a former paper published in the *Lancet* [1] it was shown that the occurrence of beriberi was intimately associated with the consumption of a diet of which white rice was the staple. This view of the origin of the disease, first stated in concise form in this country by Braddon [2], had its beginnings in the work of the Dutch physicians of the last century, and has since been amplified and confirmed by the labours of Van Dieren, Dubruel, Fletcher, and others, and more especially by the valuable observations and researches of Braddon.

Further experimentation was undertaken by us to determine the mode of operation by which white rice was able to produce this result. Braddon believed that the cause of beriberi was a poison developed in stale white rice by the action of some organism, while Dubruel held that a living germ was ingested with white rice, and that this germ, multiplying in the body, produced the disease. The observations made by us led to the conclusion that beriberi is a disorder of metabolism and that white (polished) rice, as milled by machinery on a large scale, commonly makes default in respect of some substance or substances essential for the maintenance of the normal metabolism of nerve tissues. It was further shown that in the original grain these substances are contained in the cells of the subpericarpal layers which are removed in the process of polishing. As measures for the prevention of the disease it was recommended that, for the ordinary white rice in the diet, there should be substituted a rice in which the polishing process had been omitted or carried out to a minimal extent. These conclusions, first published in December, 1909, received the endorsement of the Far Eastern Association of Tropical Medicine at its meeting in Manila in March, 1910 [3], and practical measures, based upon them, are now being taken by the Governments of those countries where beriberi most abounds.

During the past year attention has been directed towards the determination of the nature of the substances present in the subpericarpal layers of the original grain which are removed in the milling process and which, it would appear, are of such high physiological importance in maintaining normal nutrition when a diet largely composed of white polished rice is consumed. This research has not yet been completed, but thus far it has confirmed the accuracy of the work already recorded, and by a process of exclusion the problem has become appreciably less complex.

Introductory.

For the purpose of testing the value of the various materials, fowls weighing 1,200 grm. or thereabouts were employed. Each, as in previous experiments, was confined to a separate cage and, save in one instance, groups of twelve were used. The fowls received rice twice daily at 10 a.m. and 3 p.m., and when receiving polishings or materials prepared from polishings, the substance in question was given as an emulsion, by means of a stomach-tube, half an hour after the rice had been given. Every fowl was weighed once a week at 12 noon.

As a result of a series of former observations it had been determined that fowls weighing from 1,200-1,400 grm. required about 60 grm. of unpolished rice daily, and, if fed on 60 grm. polished rice, they required in addition 5 grm. of sifted polishings for the maintenance of weight and health. In a previous experiment, where products derived from different lots of padi were employed, 3·5 grm. of the polishings were shown to be sufficient with the white rice then in use. In the present experiment all the products employed—unpolished rice, polished rice, polishings, &c., were derived from the same lot of padi. For purposes of comparison the following results of analysis are given:—

	Protein	Fats	Carbohydrates	Ash	Moisture	P_2O_5
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Polishings (sifted) ..	13·7	14·16	52·77	7·54	11·83	4·1
Unpolished rice ..	9·0	1·65	75·52	1·08	12·75	0·56
Polished rice ..	8 6	0·22	76·23	0·6	14·35	0·26

When the composition of these articles is calculated on dried materials the differences are rendered more striking and accurate, and when in a similar manner the composition of a diet made up of 60 grm. of polished rice and 5 grm. of polishings is calculated it will be seen how closely such a diet approximates to one of unpolished rice.

Calculated on Dried Materials.

	Protein	Fats	Carbohydrates	Ash	P_2O_5
	Per cent.	Per cent.	Per cent.	Per cent	Per cent.
Polishings (sifted)	15·5	16·0	59·8	8·5	4·65
Unpolished rice	10·3	1·89	86·5	1·28	0·64
Polished rice	10·0	0·25	89·0	0·7	0·3
Ration, 60 grm. polished rice *plus* 5 grm. polishings, contains per cent.	10·4	1·5	86·6	1·31	0·64

Sifted polishings were invariably employed because polishings as received from the millers contain a considerable mixture of husk and broken rice.

Polishings when fresh are neutral in reaction, but on keeping they become acid. This change does not impair their efficiency, however, and polishings which have been stored with ordinary care for months are quite as valuable as the fresh materials. The ordinary process of cooking does not impair the value of polishings. For these reasons it is considered that the essential substance or substances are not unstable.

(1) *Fat.*—Fat in the rice grain is mostly confined to the subpericarpal layers. Unpolished rice is therefore richer in fat than polished rice, and polishings are very rich in fat. To determine the value of this fat a quantity of sifted polishings was packed in a percolator and percolated with petroleum ether. In this way the amount of fat in the polishings was reduced from 14·16 to 0·6 per cent. The fat-free polishings were dried by exposure to the sun until free from petroleum ether.

Twelve fowls were fed on polished rice and received in addition daily 4·5 grm. of fat-free polishings, being the approximate equivalent of 5 grm. of sifted polishings. The fowls remained healthy and maintained their weight just as had been the case when fowls received polished rice and sifted polishings. The non-importance of fat was therefore decided and its exclusion from the number of possibilities was of the utmost value since the fat had hitherto complicated our experiments.

(2) *Phytin.*—Estimations of the percentage of phosphorus pentoxide in rices had consistently shown their value as indicators of the liability or otherwise of a given rice to produce polyneuritis. Thus the higher the percentage of phosphorus pentoxide contained in a rice, the less liable was that rice to produce polyneuritis when fowls were fed on it.

The unpolished rice which we employed contained 0·56 per cent. phosphorus pentoxide and did not cause polyneuritis. The polished rice contained 0·26 per cent. phosphorus pentoxide and invariably caused polyneuritis, while washed polished rice containing 0·22 per cent. phosphorus pentoxide was more harmful than the unwashed polished rice. This suggested the probability that the essential substance was one containing phosphorus. It was first stated by Dr. Hans Aron [4], Bureau of Science, Manila, that the substance in question is phytin, the calcium magnesium salt of an organic acid containing phosphorus. We estimated that the unpolished rice in use contained 1·07 per cent. of phytin, that the polished rice contained only a trace of that salt, and that the polished rice after washing and drying contained none. The sifted polishings contained 8·8 per cent. of phytin.

In testing the importance or otherwise of phytin we did not employ the commercial product because of our ignorance of its source and method of preparation, but prepared it ourselves in the following manner. Sifted polishings were mixed with 0·3 per cent. hydrochloric acid in the proportion of 300 grm. of the former to 2,000 c.c. of the latter, the mixture was stirred throughout the day, and on the following morning was filtered through a Buchner's filter. The clear yellowish filtrate was mixed with one and a half times its volume of 95 per cent. alcohol, which produced a white precipitate of

phytin; the mixture was allowed to stand for a few days. The precipitate was collected, washed with strong alcohol to free it from acid and dried in a vacuum desiccator. A friable cake of phytin was obtained readily reducible to a white powder, soluble in water, yielding an opalescent solution with an acid reaction and giving, on addition of sodium carbonate, a white flocculent precipitate. The powder contained 34 per cent. of phosphorus pentoxide.

A fowl consuming 60 grm. of unpolished rice daily would be receiving 0·66 grm. of phytin, and a fowl receiving the same amount of washed, polished, and therefore phytin-free, rice would require to have in addition that amount of phytin daily in order to bring the value of this diet, in respect of phytin, up to that of an unpolished rice diet.

Twelve fowls received washed, polished rice, and in addition phytin, which was given in the following manner: 9 grm. of phytin were dissolved in distilled water, the solution neutralized with sodium carbonate, and the volume made up to 360 c.c. Each fowl received 15 c.c. of this suspension at 10.30 a.m. and 3.30 p.m. daily, an amount of phytin slightly in excess of the estimated quantity. All the fowls lost weight and cases of polyneuritis occurred just as if the fowls had received washed, polished rice only.

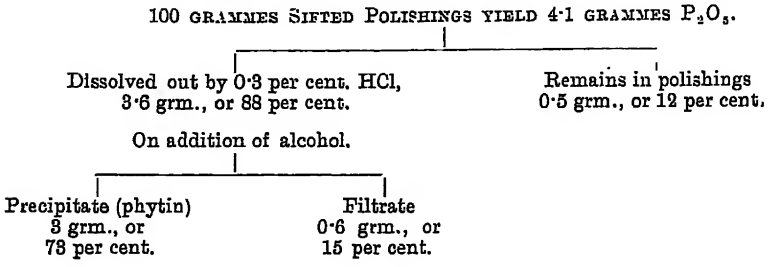
In the next experiment twelve fowls received the phytin suspension intimately mixed with the washed, polished rice, but the results were the same, and the importance of phytin in the prevention of polyneuritis was by these experiments definitely disproved.

(3) *Substances soluble in* 0·3 *per cent. hydrochloric acid.*—Experiments were next carried out to determine if, when polishings are macerated in 0·3 per cent. hydrochloric acid the essential substance or substances pass into solution. This solvent was chosen as it had been employed for the extraction of phytin. Polishings in quantities of 180 grm., being the amount required by twelve fowls in three days, were mixed with 1,000 c.c. of 0·3 per cent. hydrochloric acid stirred during the day, and the following morning filtered through a Buchner's filter. 100 c.c. of 0·3 per cent. hydrochloric acid were used to wash out the vessels. When fluid could no longer be extracted from the mass it was mixed with 600 c.c. of 0·3 per cent. hydrochloric acid, stirred during two hours, and thereafter filtered as before. The extracted polishings were mixed with distilled water, nearly neutralized with sodium carbonate, and the volume was adjusted to 1080 c.c.; 30 c.c. of this emulsion contained 5 grm. of polishing, less the materials dissolved out by the acidulated water. The combined filtrates obtained from 180 grm. of polishings were nearly neutralized with sodium carbonate and concentrated at a low temperature to a volume of 1,080 c.c. Thirty c.c. of this suspension contained the substances dissolved out by acidulated water from 5 grm. of polishings.

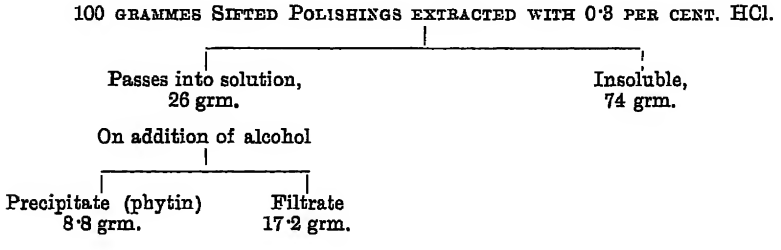
Twelve fowls were fed on washed, polished rice, each receiving daily 30 c.c. of the emulsion of extracted polishings; cases of polyneuritis occurred.

Twelve fowls were fed on washed, polished rice, each receiving in addition 30 c.c. of the suspension of dissolved substances; cases of polyneuritis did not occur. Therefore the essential material was removed and uninjured by the

process of extraction and subsequent treatment. By this process of extraction 88 per cent. of the phosphorus pentoxide contained in polishings is dissolved out. Of this amount 73 per cent. is represented by the phytin in the solution, so that, together with the 12 per cent. remaining in the polishings after extraction, 85 per cent. of the phosphorus pentoxide contained in polishings is shown to be unimportant.



(4) *Alcohol (proof spirit) soluble fraction* of the substances originally soluble in 0·3 per cent. hydrochloric acid. When 100 grm. of polishings are extracted in the manner described, 26 grm. pass into solution, and of that amount 8·8 grm. are precipitated on the addition of alcohol. Therefore, in the alcoholic filtrate which contains 17·2 grm. of the soluble substances obtained from polishings the essential material should be contained.



Experiments were next carried out to test the accuracy of this suggestion. Polishings in quantities of 180 grm. were treated as in the previous experiment, and the combined filtrates from each 180 grm. were mixed with one and a half times their volume of 95 per cent. alcohol. After standing for two days the precipitate was filtered off, dissolved in warm distilled water, nearly neutralized with sodium carbonate, and the volume adjusted to 1080 c.c., 30 c.c. of this suspension contained the alcohol precipitable substances (phytin) from 5 grm. of polishings.

Six fowls were fed on washed polished rice and received daily 30 c.c. of this suspension of phytin. Cases of polyneuritis occurred, thus confirming the accuracy of the previously recorded experiments which proved that phytin was unimportant.

The alcoholic filtrate was nearly neutralized with sodium carbonate and evaporated at a low temperature until free from alcohol. The residue was diluted with distilled water to a volume of 1080 c.c. 30 c.c. of this suspension contained the almost phytin-free soluble substances from 5 grm. of polishings.

Six fowls were fed on washed polished rice, and each received daily 30 c.c. of this suspension. All remained healthy.

These experiments prove that of 5 grm. of sifted polishings required daily for the maintenance of weight and health in a fowl on a white polished rice diet, no less than 4·2 grm. are unimportant, and of the 0·8 grm. remaining probably only a part is essential.

	Effect on fowls; estimated by occurrence of polyneuritis	Estimated percentage of fat in diet	Estimated percentage of P_2O_5 in diet
Unpolished rice	−	1·65	0·36
Polished rice, plus polishings	−	1·3	0·55
Polished rice	+	0·22	0·26
Washed polished rice	+	0·22	0 21
Washed polished rice, plus fat-free polishings	−	0·25	0·51
Washed polished rice, plus polishings	−	1·3	0·51
Polishings extracted with 0·3 per cent. HCl :—			
Washed polished rice, plus extracted polishings	+	1·3	0·23
Washed polished rice, plus extract :—			
Extract mixed with one and a-half times its volume of 95 per cent. alcohol	−	0·22	0·47
Washed polished rice plus precipitate (phytin)	+	0·22	0·41
Washed polished rice plus filtrate	−	0·22	0·24

Summary and Conclusions.

(1) White polished rice when forming the staple of the diet in man has been shown to cause beriberi.

(2) Such white polished rice when fed to fowls produces in them a disease closely analogous to beriberi in man. This reaction has been taken in this, and previous researches, as a test of the beriberi producing power of a given rice when it forms the staple of a diet in man.

(3) The addition of rice polishings to a diet of white rice is an effective preventive of the development of polyneuritis in fowls. Rice polishings comprise from 8 to 10 per cent. by weight of the original grain.

(4) The substances contained in polishings which are effective in preventing polyneuritis, are soluble in 0·3 per cent. hydrochloric acid, and are not precipitated from the solution on the addition of 95 per cent. alcohol in quantity sufficient to make the resulting mixture of proof-spirit strength. These sub-

stances comprise 16 per cent., or less, by weight of rice polishings, or 1·6 per cent., or less, by weight of the original unpolished rice grain.

(5) The fats, which are contained in rice polishings in comparative abundance, have been proved of no importance in preventing polyneuritis.

(6) Phosphorus compounds equal to 85 per cent. of the total phosphorus content have been proved to be unimportant in preventing polyneuritis.

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Annual Report, Institute for Medical Research,
for the year 1910.

Beriberi.

Several observers have now confirmed the accuracy of the observations, originally made in this country by Dr. Braddon, that a diet in which white rice unduly preponderates results in the production of beriberi, and that a diet of parboiled rice is an effective preventive of the disease.

Dr. Braddon believed that the cause of beriberi was a poison developed in stale white rice by the action of some micro-organism, and that in the parboiling process these organisms are made to germinate and in that vulnerable stage are destroyed.

Further work has cast doubt on the accuracy of this hypothesis to explain the origin of beriberi. In a paper read before the Far Eastern Association of Tropical Medicine, on the results of a series of observations made at this Institute, the view was advanced that beriberi was a disorder of metabolism and that, in the preparation of white rice by machinery, substances essential for the maintenance of health were removed from the grain. As a measure for the prevention of the disease, it was recommended that, for the ordinary white rice, there should be substituted unmilled rice, or rice in which the milling process has been carried out to the minimal extent. According to this view parboiled rice comes into the general class of unpolished rices. Papers advocating similar views were submitted to the Congress by Drs. De Hann, of Java, H. Campbell Highet, of Siam, and Hans Aron, of Manila. As a result of the discussion which ensued, the following resolution was passed:—

Resolved, that in the opinion of this Association sufficient evidence has now been produced in support of the view that beriberi is associated with the continuous consumption of white polished rice as the staple article of diet, and the Association accordingly desires to bring this matter to the notice of the various Governments concerned.

During the past year attention has been directed towards the determination of the nature of the substances present in the subpericarpal layers of the grain removed in the whitening process and which, it would appear, are of such high physiological importance in maintaining normal nutrition when a diet largely composed of white polished rice is consumed. This research, which is still in progress, has thus far confirmed the accuracy of the results already recorded and by a process of exclusion the problem has become appreciably less complex. It has been found that fats which are contained in rice polishings in comparative abundance are of no value in preventing poly-

neuritis and that compounds of phosphorus equal to 85 per cent. of the total phosphorus content are similarly unimportant.

The effective substances have been shown to be soluble in 0·3 per cent. hydrochloric acid. They are not precipitated from this solution on the addition of 95 per cent. alcohol in sufficient quantity to make the resulting mixture of proof spirit strength. These substances comprise 1·6 per cent. or less by weight of the unpolished rice grain. Further researches are being carried out and a report on the results obtained will be furnished shortly.

It seems probable in view of the results already obtained in these researches that the methods of constructing artificial diet tables will require to be revised. It would appear that there are factors entering into the composition of food-stuffs which are of more complex nature than their protein, fat or carbohydrate content or their calorific value, and there is reason to hope that with the advance of knowledge in physiological chemistry entirely new principles in the causation and prevention of disease may be discovered.

Studies from the Institute for Medical Research, No. 12, 1911.

The Etiology of Beriberi.

Introduction.

The etiology of beriberi has been the subject of investigation by workers in many countries, and from the wide divergence of the conclusions arrived at and the varying results of preventive measures, it will be apparent that the problem is one of great complexity. Not a little confusion has been introduced by the lack of agreement among authorities as to what disease conditions are to be included under the name beriberi. A survey of the voluminous literature which concerns itself with this disease will show not only that forms of polyneuritis of different etiology have been called beriberi, but that even diseases of which polyneuritis may not be a prominent feature such as "epidemic dropsy," "ship beriberi," "Ceylon beriberi," and the like have been included under this name. It is not to be expected, therefore; that any single etiological factor will satisfactorily explain all the recorded outbreaks of beriberi.

Malaya has long been known as an "endemic focus" of beriberi and the recorded sickness and mortality rates from that disease during several decades show that great economic losses have resulted from its ravages. The Government of the Federated Malay States has greatly interested itself in furthering investigation into the cause of beriberi and five years ago the task was assigned to us of attempting to define more narrowly the etiological factors concerned. In previous papers the results of this work as obtained from time to time have been set forth and it is now proposed to review the progress made and to submit the details of the work upon which our conclusions are based.

Historical.

At the time this inquiry was begun, students of the disease were divided into two principal groups in regard to their views of its origin. On the one hand it was held that beriberi had its origin in some organism, bacterial or protozoal, and that the disease was communicable, directly or indirectly, from man to man; on the other hand it was maintained, more particularly by physicians in Eastern Asia where the disease is most common, that the cause of beriberi was to be sought for in food.

An examination of the evidence put forward by these latter workers, notably Takaki in Japan, Eijkman, Grijns, Vorderman and others in the Dutch East Indies, and Braddon in this country, made it difficult not to believe that diet

was a factor of great importance in the causation of beriberi and that inquiry along this line held out the best prospect of success.

Attention was directed long ago to the influence of diet in the causation of beriberi. Wernich (1878), who studied the disease in Japan, says :—

The kakké is a chronic constitutional disorder of blood-making and of the vascular system. Rice as the exclusive food of the people is answerable for it in a quite especial way. Not, however, as some have thought because it is used in a decomposed state, but because it is used in such quantities that the power of assimilation is gradually lost for other kinds of food ; and even the large quantity of rice is unable to render the nutrition and blood-making adequate.

Van Leent (1880), from his experiences in the Dutch East Indies, wrote :—

The dietetic error which I regard as the one and only cause of the morbid composition of the blood in beriberi consists in the too small proportion of albuminous substances and fat.

In support of this he gives the experiences of the disease in the Dutch East Indian fleet from 1870 to 1878 particularly during the war in Acheen both among the native and European members of the crews.

Takaki (1885) believed the disease to be due essentially to nitrogen starvation and introduced certain reforms in the diet of the Japanese Navy. Up to this time beriberi had been an important source of invaliding and mortality among the sailors, of whom about 30 per cent. were incapacitated annually from that disease. By the beginning of 1890, under the improved diet, beriberi was wholly eradicated and the incidence of other diseases greatly decreased. Takaki (1906) still adheres to this view of beriberi causation and in the course of a series of lectures on "The Health of the Japanese Navy and Army" he gives fresh evidence in its support :—

Another illustration of the influence of diet upon the health of the men is shown by the fact that there was not one case of beriberi among the sailors of the naval brigade before Port Arthur although there was a large number of cases in the army. These men lived among the soldiers and under exactly the same conditions but they differed from the soldiers in one respect that they were supplied with one pound of meat, ten ounces of barley, and twenty ounces of rice *per diem* while the soldiers were supplied with five ounces of meat and thirty ounces of rice. The above example confirms my view that beriberi largely occurs among men who are fed with an insufficient quantity of nitrogenous food and an excess of carbohydrates.

Durham (1904), who studied the disease on Christmas Island and in the Malay Peninsula says :—

So far as there was any semblance of a positive result in the observations it is suggestive that beriberi is communicated from person to person more or less directly or through fomites as an actual infection. It was difficult not to believe that the presence of some constituent of the diet had a sheltering effect on the nervous system of the individual. It is suggested that certain articles of diet by virtue especially of containing phosphorized and fatty matters may tend to ward off the disease when given in sufficient amount.

Bryce (1907) quotes Professor Chittenden of Yale as saying :—

With regard to the statement that the Japanese Navy had found that a high protein diet was accompanied by a diminution in the number of cases of beriberi he contended that it did not necessarily follow that the increase of protein was the cause. He thought that it was much more likely that other elements were introduced into the food capable of accounting for the disappearance of the disease. Protein pure and simple is unlikely to be utilized as a food in the body. It is much more likely that it requires to become a salt of lime, potash or soda

before it can be available for dietetic purposes. He thinks the mineral salts introduced with the protein prevented beriberi much in the same way that lemon-juice prevents the appearance of scurvy.

The incidence of beriberi is certainly greatest in those tropical and sub-tropical countries whose inhabitants partake of a diet in which rice forms an important and generally the staple constituent. The other articles of diet vary with the country but rice varies merely in kind or quality and but little in regard to the quantity consumed.

In those countries where the disease is prevalent the incidence has always been greatest among the poorer classes and among inmates of public institutions. Supporters of dietary hypotheses have therefore sought to account for the occurrence of the disease in that the diet consumed was deficient and those who have incriminated rice consider that a diet in which this article bulks largely may be deficient in protein or fat, or that the rice has become diseased from the action of moulds or other organisms.

The suggestion of a relationship between a rice diet and beriberi is a very old one and there are numerous references to it in the literature of the disease. Hirsch (1881), in a review given of the various hypotheses propounded to explain the origin of beriberi, says :—

The conjecture that the morbid poison is some *specifically noxious thing in the food*, brought about by the local conditions, is a probable one, and there has been no lack of hypotheses in that sense. At an early period the question was propounded whether it might not be some *noisonous property of (decomposed) rice* that represented the cause of the malady.

This conjecture was revived by Braddon (1901) who studied the disease in the Federated Malay States, and his studies have led to material advances in our knowledge. Braddon was the first to show the closeness of the relationship which exists in this country between the consumption of white rice as a staple article of diet and the disease beriberi. Of even greater importance was his demonstration of the fact that where the staple article of diet is rice which had been parboiled before husking as used by the Tamil population, or rice as prepared by the Kampong Malays, the disease does not occur. As will presently appear this position which for many years Braddon defended in local medical circles has since been abundantly justified by controlled experiments.

Braddon's conception of the mechanism of beriberi causation through white rice (" stale uncured rice ") was that

The cause of the disorder is not indeed rice, *qua* rice, or as an article of diet, but diseased rice; rice with which poison derived from decay, due perhaps to some fungus, or mould, or germ, or spore, originally perhaps growing upon the husk, has become mixed during the process of milling; or upon which such fungus may have grown and such poison have been produced after decortication.

In accordance with this hypothesis Braddon recommended as preventive measures the use of fresh rice (Malay rice or freshly milled rice), or rice that had been parboiled before husking. He conjectures that in the parboiling process, the hypothetical organisms are made to germinate and in that vulnerable stage are destroyed by heating. He compares the process with that employed

in laboratories to sterilize or render free of noxious germs various materials which may contain them.

This hypothesis of beriberi causation has not met with acceptance by later investigators, Grijns, Kiewit de Jonge, Schaumann, Aron and ourselves, who regard the disease as the result of some defect in the composition of the food-stuffs ingested.

Human Feeding Experiments.

With a view to determine the position of white rice in regard to the causation of beriberi, Fletcher (1907) carried out a series of observations extending over two years among the patients in the Lunatic Asylum, Kuala Lumpur. In his report of the results Fletcher says:—

During the year 1905 a large number of lunatics in the Kuala Lumpur Lunatic Asylum suffered from beriberi. Ninety-four of the 219 lunatics treated in the asylum were affected and twenty-seven died from the disease. With the purpose of testing Dr. Braddon's theory, observations were carried on in the following years (1906, 1907) with regard to the diet of the patients. Half of the patients were placed on a diet of "cured" (parboiled) rice while the other half remained on the diet of "uncured" (white polished) rice which kind all the lunatics in the asylum had been eating previous to the commencement of the observations. The lunatics were housed in two exactly similar buildings on opposite sides of a quadrangle surrounded by a high wall. On December 5, 1905, all the lunatics at that time in the hospital were drawn up in the dining shed and numbered off from the left. The odd numbers were subsequently domiciled in the ward on the east side of the courtyard and no alteration was made in the diet; they were still supplied with the same uncured rice as in 1905. The even numbers were quartered in the ward on the west side of the quadrangle and received the same rations as the occupants of the other ward, with the exception that they were supplied with "cured" rice instead of the "uncured' variety. The two batches of patients were kept in separate wards and fed at different times. Separate cooking and feeding utensils were used but otherwise the patients were allowed to associate together. At the half year the two batches were changed over to each others' apartments.

The result for 1906 was that

Out of 124 inmates fed on "uncured" rice, thirty-four suffered from beriberi, two of whom were suffering from the disease on admission, and eighteen died; whereas among 128 inmates fed on cured rice there were only two cases of beriberi, both of whom were suffering from the disease on admission, and no deaths.

At the end of 1906 there remained thirty-five lunatics in the "cured" rice ward and thirty in the "uncured" rice ward. The first patient admitted in 1907 was admitted to "uncured" rice, the second to "cured," the third to uncured and so on to the end of the year.

During the year 1907, 136 patients were treated in the "uncured" rice ward; of these patients twenty-eight suffered from beriberi, four of whom were suffering from the disease on their admission. During the same year 131 patients received a diet containing "cured" rice; four of them were admitted actually suffering from beriberi but none of these 131 patients developed the disease in the asylum.

Fletcher concludes that:—

The cause of beriberi is to be sought for in the diet. The result of the experiment tends to show that white polished rice, although of the best quality, is a cause of beriberi acting

either by some poison which it contains or by a starvation due to some defect in the nutritive value of such rice.

In 1907-1908 the writers (Fraser and Stanton, 1909) carried out a series of observations designed to test the position of white rice as a causative agent in the production of beriberi. The results may here be summarized.

It was considered important that these observations should be made in a place hitherto free from the disease and where the operation of factors other than diet could be excluded or adequately controlled. Satisfactory conditions were obtained at Durian Tipus in Negri Sembilan where some 300 Javanese labourers were engaged in the construction of a new road through virgin jungle, remote from the complex conditions which interfere with observations in populous areas. The quarters occupied by these labourers were new and the sanitary conditions satisfactory.

The 300 labourers were divided into two parties of approximately equal numbers and were housed some miles apart. Before beginning the experiment an examination was made of each person and the presence of cases of existing or recent beriberi was thereby excluded.

To one party white rice (No. 2 Siam) was issued as the staple article of diet, and to the other party parboiled rice. In about three months cases of beriberi began to occur among the members of the party on white rice. When a certain number of cases had been noted white rice was discontinued and thereafter no cases occurred. No sign of the disease appeared among the control party on parboiled rice.

The conditions were then reversed. The party hitherto on parboiled rice were given white rice and after a somewhat longer interval than in the first series of experiments, beriberi broke out in this group also. This outbreak ceased on discontinuing the issue of white rice. Again no sign of the disease appeared among the control party on parboiled rice. By the transfer of individuals suffering from beriberi and of whole groups in which the disease was occurring it was found possible to test the influence of place considered as a nidus of infection and also to test whether the disease was communicable from one individual to another.

The average daily ration was as follows :—

Rice	21·3 oz.	603 grammes
Dried Salt Fish ...	4·25 ,,	120 ,,
Onions	1·75 ,,	50 ,,
Potatoes	1·75 ,,	50 ,,
Coconut oil ...	0·85 ,,	24 ,,
Coconut	1·50 ,,	42 ,,
Tea	0·12 ,,	3·4 ,,
Salt	0·1 ,,	2·8 ,,

In a recent publication Dr. H. Schaumann (1910) has dealt with the composition of this diet and quotes the results in support of his view that the disease beriberi is due to a diet defective in substances having a high organi-

cally-combined phosphorus content. As Dr. Schaumann has assigned values to the various foodstuffs comprising this diet which differ from those given by us it would appear that he had not before him a copy of the publication in which these were furnished.

The analyses upon which our calculations were based were carried out with the actual foodstuffs employed, and were not taken upon the authority of a textbook on dietetics. We feel called upon to make this explanation as a protest against the use of analyses of foodstuffs given in textbooks, however eminent the authority, for the calculation of the relative values of diets. As we shall hope to show later, fundamental differences may exist in the nutritive value of various combinations of foodstuffs which are not revealed by the ordinary methods of analysis and there are factors in the composition of food which are of much more complex nature than its protein, fat and carbohydrate content or its calorific value.

Whatever methods of analysis are employed it may be well that the defect of nutrition, which we regard as the cause of beriberi, will escape observation but certainly it appears that when the actual foodstuffs issued in a diet are not the subject of analysis, the results are not likely to help materially towards a solution of the problem of beriberi causation.

Our observations have shown that beriberi is definitely associated with the consumption of a diet of which white rice is the staple. It must be due either to a poison contained in white rice or to a deficiency in such a diet of some element of high physiological value. If the latter, then accuracy is imperative and can only be attained by analysis of the actual foodstuffs eaten by those among whom the disease occurred. So far as we are aware such an opportunity has only been afforded by our planned observations now under discussion.

The various articles composing the diet issued were submitted to analysis in this Institute by Mr. B. J. Eaton.

The average of a considerable number of analyses was as follows:—

	Moisture Per cent.	Protein Per cent.	Fat Per cent.	Carbohydrate Per cent.	Ash Per cent.
White rice	13·85	7·45	0·17	78·02	0·51
Parboiled rice ...	14·03	7·8	0·53	76·92	0·72
Dried salt fish ...	48·1	35·7	2·96		13·24
Onions	86·44	1·5	0·28	11·28	0·5
Potatoes	65·3	1·8	0·2	31·66	1·04
Coconut	45·3	3·95	34·6	15·2	0·95

Based on these analyses the diet issued to those on white rice as the staple was calculated to consist of:—

Protein	Fat	Carbohydrate	Salts
91·45 grm.	43·70 grm.	499·16 grm.	23·06 grm.

The diet issued to those on parboiled rice was calculated to consist of:—

Protein	Fat	Carbohydrate	Salts
93·56 grm.	45·88 grm.	492·54 grm.	24·33 grm.

It is generally accepted that the dietary requirements per kilogramme of body weight are protein 2 grm., fat 1·5 grm., carbohydrate 6 grm. salt 0·5 grm. The average body weight of the people under our observation was 100 lb, nearly. The diet should therefore contain :—

Protein	Fat	Carbohydrate	Salt
90 grm.	68 grm.	272 grm.	20 grm.

Comparison of this calculated standard diet with the diets consumed by the persons under observation will show that the issued diets cannot be regarded as deficient save in respect of fats. This latter deficiency is, however, more than compensated for by the excess of carbohydrates. With a sufficiency of protein in a diet, fats and carbohydrates are to a great extent interchangeable and the inhabitants of warm countries habitually consume less fat and more carbohydrate than do the inhabitants of cold countries.

It will be noted that the analyses of these foodstuffs did not include an estimation of the relative proportions of the inorganic salts composing the ash, nor did they take account of the manner of combination organic or inorganic, in which these substances originally existed in the rice grain. This matter will be referred to in some detail at a later stage of this report.

The conclusions arrived at in this inquiry were stated as follows :—

(1) In the course of a systematic inquiry especially undertaken to test the position of white rice as a causative agent in beriberi it was observed that twenty cases of this disease, occurred among 220 people on white rice who were continuously present in the various parties during the course of the outbreaks. In the parties on parboiled rice during the same periods and under similar conditions, among 273 people no sign of the disease appeared.

(2) Since all cases presenting doubtful signs of the disease were excluded we are of opinion that there were many other cases which in the ordinary routine of clinical practice would have been regarded as beriberi. Such cases only occurred among those who consumed white rice and their inclusion would not strengthen the case for an infectious origin of the disease.

(3) No case of beriberi occurred in any person who had been on white rice for less than eighty-seven days.

(4) Systematic examinations were made of the blood and urine of patients suffering from beriberi. Various methods of examination were employed but in no case were organisms found other than those well known as the causative agents of other diseases.

(5) In the course of the inquiry patients in various stages of beriberi were in contact with parties of men on parboiled rice. The results of observations made on such occasions furnished evidence that the disease is not a communicable one.

(6) Removal of patients from the place where they had contracted beriberi did not influence the progress of the disease and the removal of entire parties from the place where the disease had occurred did not influence the progress of an outbreak so long as they continued on white rice. These

observations suggest that place *per se* or considered as a nidus of infection has no influence upon the development of beriberi.

(7) In three instances in which definite outbreaks of beriberi occurred among parties of men on white rice, substitution of parboiled rice was followed by cessation of the outbreak.

(8) The occurrence of beriberi cannot be attributed to deficiency in the diet issued in respect of either protein, fat, carbohydrate or salts as estimated by the methods in common use.

(9) No evidence was obtained to show that any article of the diet other than white rice was responsible for the occurrence of beriberi.

(10) Ankylostomes and other nematode worms were not found in a larger proportion of patients suffering from beriberi than in the general population under observation.

(11) The general results support the view that the disease beriberi as it occurs in the Malay Peninsula has an intimate relationship with the consumption of white rice and further research along these lines is justified.

On April 26, 1909, Dr. J. D. Gimlette reported to the Senior Medical Officer, Selangor, that a number of Malays recently enlisted into the Police Force and then stationed at the depot, Kuala Lumpur, had reported themselves sick. On examination Dr. Gimlette had found that they were suffering from beriberi. He adds: "The occurrence is of interest because it has been possible to recognize the disease in an early stage. The majority of those attacked are newcomers who have recently fallen ill while their rice (No. 2 Siam) has, I understand, only recently been supplied through a new subcontractor. The patients are all Malays with one exception, a Javanese."

The rice was changed from white polished rice to parboiled rice on April 27, and on June 2, Dr. Gimlette reported that the occurrence of the disease had ceased and that no deaths had occurred among those suffering from beriberi.

Through the courtesy of Dr. Gimlette and Dr. Freer, Senior Medical Officer, Selangor, we were enabled to obtain a bag of the white rice which was in use at the Police Depot at the time of the outbreak of beriberi.

Throughout the course of our inquiry at Durian Tipus samples of the white rice issued were collected daily and forwarded to the Institute.

So far as the laboratory aspect of the question was concerned therefore, an abundant supply of the rices which actually caused these outbreaks of beriberi was secured. In connection with the plan of work which we had formed we regard this circumstance as of the first importance. It could have led to no real advance in knowledge if analyses of a series of rices from various sources had been carried out without regard to their connection with outbreaks of beriberi. Having first shown that the consumption of a certain white rice was the cause of an outbreak of beriberi we were in a position to proceed further and by analysis of and experiments with that rice to seek for the explanation of this relationship. The continuity of work thereby established we believe to be a principal merit of the observations here recorded.

Rice.

The cultivation of rice has existed from ancient times. It is a cereal indigenous to certain areas in both hemispheres, but its culture now extends over wide areas in tropical and subtropical countries possessing an assured and heavy rainfall; also with the aid of irrigation, cultivation has been extended to areas not possessed of a sufficient rainfall. The operation of these factors has produced many species and varieties of rice so that their number is now very great. We are not in a position to treat this subject in a comprehensive way and must of necessity confine our remarks to the countries and their rices which have come under our immediate observation.

In the Straits Settlements and Federated Malay States a limited amount of rice is grown. The quantity is quite inadequate to supply the demand of a country which is rapidly and extensively being opened up and therefore supplies have to be imported from the great producing countries, more especially Siam, Burma and French Indo-China.

Rice is derived from the fruit, botanically a caryopsis, of plants belonging to the genus *Oryza*. The product as it reaches this country is in the form of unhusked fruit (padi), the partially husked fruit (cargo rice) or the finished product (rice).

The imported unhusked or partially husked grain is converted into rice in the mills of Penang and Singapore. So far as can be ascertained the principal reason for the importation of the unfinished product is that parboiled rice may be prepared locally and sold at a lower price than the parboiled rice imported from India. The local mills are also able to produce ordinary white rice, and the question as to which variety of rice a mill shall produce is answered by the demand.

Malays in the country districts grow the grain in quantities sufficient for their own requirements, and from it prepare the rice by primitive methods of pounding and winnowing.

Immigrants, natives of India, China and Java, come to this country either as workers on mines or on estates, and therefore have not opportunities for growing the rice they require. The immigrant Indians are for the most part recruited from the south of India and prefer parboiled rice, which must be cheap. It is to meet this demand that the large rice mills of Penang, Singapore and Perak have been called into existence. The natives of China and Java prefer a rice which has not been parboiled, and for their requirements the grain is husked and polished by machinery. The product is commercially known as Rangoon, Siam, or as we prefer to call it here, white rice.

The kinds or forms of rice used in this country may therefore for purposes of this account be called (1) parboiled rice; (2) white rice; and (3) Malay rice.

(1) Parboiled Rice.

As prepared in the large power-mills the grain is soaked in water for twenty-four to forty-eight hours, the water is then run off and the grain is transferred to cylinders which are lightly covered and steam is passed through the contents for five or ten minutes. The grain is thereafter transferred to open paved courts and dried in the sun. The husk is now more readily detached than in the untreated grain, but the contents of the grain have been rendered tough and semi-translucent.

In the milling of this parboiled grain the husk is removed and the rice is subjected to a limited amount of pearling or polishing in a machine provided with stone facings. By no process can such rice be made to appear white, consequently polishing is as a rule employed merely to complete the removal of fragments of husk and most of the pericarp.

Parboiled rice is also prepared on a less pretentious scale in small mills not provided with steam plant. The product is similar to that produced in the larger mills, but in view of the insanitary conditions prevailing in many of these places, numbers of them have been compulsorily closed. Parboiled rice prepared in this manner has a peculiar disagreeable penetrating odour caused by the preliminary soaking in cold water; by soaking the grain in hot water in place of cold water and for a shorter period, the occurrence of this disagreeable odour can be prevented.

Other millers have sought to improve their product by subjecting the grain to more extensive polishing or pearling; as will be shown later, this may be attended with dangerous results to those who consume such a highly-polished parboiled rice as the staple of their diet.

According to Hooper (1909) rice in Bengal is treated before husking by three methods:—

(1) Hot water is sprinkled over the padi.

(2) The padi is soaked in cold water for twenty-four hours.

(3) The padi is first soaked in water and afterwards boiled.

In each case the padi is thereafter dried in the sun or by other means. When the grains are sufficiently dry they are husked in a pestle and mortar.

Watt (1908) states that "In India a large part of the rice sold in shops and exported to Europe as an article of food has been prepared by being first half boiled then dried in the sun and finally husked by the ordinary pestle and mortar. Such rice is in trade termed 'parboiled.' Husking without boiling is a very tedious process when done by hand." According to the same authority, in India proper, power mills for the preparation of rice are very few in number. In 1904 there were in all India 127 rice mills with 17,814 employees, and of this number 114 mills with 17,016 employees were located in Burma.

Parboiled rice prepared in India has no objectionable odour. It is imported into this country to a limited extent for consumption by the more wealthy natives of India.

The objectionable odour of locally prepared parboiled rice has hitherto militated against its more widespread use by other than natives of India, and if the consumption of parboiled rice is to be encouraged such improvements in the process are required as will produce a rice similar to the parboiled product of India.

(2) White Rice.

In the milling of white rice in large power mills the padi is first deprived of the husk. This is done by passing it into a machine called the "huller" which has two iron discs faced with a cement of which emery is one of the ingredients. The padi enters in a stream at the centre and is driven by centrifugal action between the discs to the periphery. By this means the husk is cracked. The mixed rice and husk are now passed over the winnowing fans which blow away the husk.

The grain still covered with its brown, yellowish or other coloured pericarp now passes to a machine in which the whitening process takes place. This machine contains a conical drum revolving at a high rate of speed; the drum is faced with emery cement and is surrounded by a casing lined with steel wirecloth. In the more modern mills the space between the cone and the wirecloth through which the rice passes can be altered by vertical adjustment of the spindle so that any required amount of attrition of the rice can be secured. In this process the fruit wall or pericarp, the layers subjacent to it (the subpericarpal layers) as well as the embryo are removed.

The whitened grain now passes to the "polisher" which contains a revolving conical drum covered with strips of sheepskin, the whole surrounded by a casing lined with wire-cloth. The polishing is accomplished as the rice passes between the sheep-skins and wire-cloth.

In the milling and polishing machines the rice meal or "polishings" passes through the wire-cloth casings and is collected. Rice polishings are commonly used as food for cattle and pigs. We are informed that natives in the neighbourhood of rice mills in Burma consume rice meal in the form of gruel.

White rice is graded commercially as Rangoon and Siam, also in accordance with the unbroken condition of the grains as No. 1 quality, or the grain mixed with broken grains as No. 2 quality and so on. Siam rice of the best quality is a long slender grain, almost white and free from dust. Rangoon rice of the best quality is a shorter and more plump grain, white and free from dust.

We should be glad if it could be made clear that in using these trade terms we do so merely as a convenience and with no intention to suggest that the padi produced in Indo-China or Siam is inferior to that produced elsewhere. A certain type of grain in commerce has come to be associated with these names, and in our use of the terms we do not mean to suggest that they necessarily indicate the country of origin of the rices used in our experiments. With the important questions of the nutritive values of different kinds of padi and the influence thereon of soil, climate, and methods of cultivation we have not concerned ourselves.

(3) Malay or Native Rice.

This is prepared from the grain grown by the Malays. The preparation of the rice is carried out by women in quantities sufficient for the immediate wants of the household. The unhusked grain is sun-dried and transferred in suitable quantities to a wooden mortar fitted with a long wooden pestle. The grain is pounded until the husks are detached and these are removed by winnowing. By repeated pounding and winnowing the husk is entirely removed as well as the greater part of the pericarp, but the subjacent layers are lost only to a limited extent by attrition and bruising. The finished product is yellowish and is an admixture of broken and unbroken grains.

By repeated pounding and careful hand-picking it is possible to obtain a fairly white rice free from unbroken grains, but the labour entailed is considerable and the natives are usually quite satisfied with a rice from which the entire husk and most of the pericarp have been removed.

Structure of the Rice Grain.

In order to compare the different kinds of rice as to their histological characters and to examine rices from beriberi outbreaks for the presence of organisms, it was necessary to obtain entire sections of the grain of sufficient thinness. The following process was devised and found to yield suitable sections.

The grains were softened for about a month in a mucilage composed of:—

Gum acacia	4 pts.
Solution of carbolic acid (5 per cent.)...	6 „

The softened grains freed from excess of mucilage were then imbedded in celloidin. The imbedded grains were placed in alcohol (60 per cent.) and after a few days were ready for cutting.

Sections were examined for moulds and for this purpose were stained by the following method:

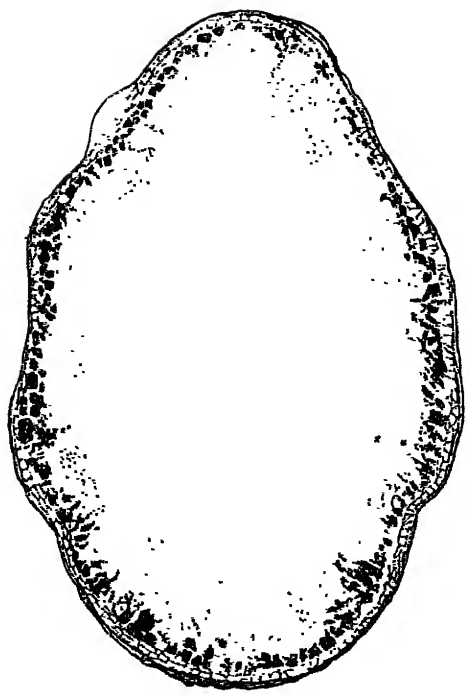
The sections were stained in anilin-gentian violet solution for from five to ten minutes. They were then freed from excess of stain and treated with Gram's iodine solution for one minute.

Excess of iodine solution was removed and the sections washed in absolute alcohol as long as stain continued to come away.

They were then treated with anilin oil for five minutes. Excess of oil was removed and the sections mounted in Canada balsam.

Plates IV, V and VI, are drawn from actual specimens and reproduce the coloration taken up by the various tissues by this method.

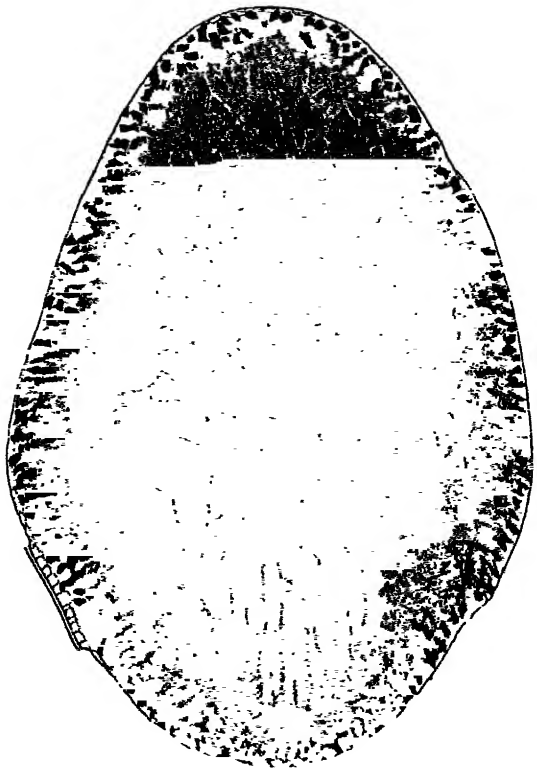
A large number of sections from various kinds of rice were examined in this way. In none of them were moulds or fungi recognized, but the method produced excellent differentiation of the tissues and it was easily possible to appreciate the histological differences between Padi, Parboiled Rice, White Rice and Malay Rice.



UNMILLED RICE.

PLATE V.

OVER-MILLED RICE.



UNDER-MILLED RICE.

A cross section of a rice grain from which the paleæ (husk) has been removed shows three zones (Plate IV) :—

(1) The outer thin pericarp.

(2) The layers subjacent to the pericarp, or subpericarpal layers, composed of cells filled with aleurone and fat and comparatively free from starch grains.

(3) The remainder of the section, the major part, composed of cells filled with starch grains.

If sections of a rice grain are treated with any of the ordinary stains for fat, such as osmic acid or Sudan III, it will be seen that fat is practically confined to the second zone or subpericarpal layers: a few scattered oil globules may be recognized in the central or starch zone.

Section of a polished rice grain (Plate V) shows that the pericarp and most of the subpericarpal layers have been removed. There is usually only a remnant of the fat and aleurone layer and sometimes not even that remains, the section consisting almost entirely of starch cells.

Section of parboiled rice (Plate VI), if the grain has not been subjected to excessive pearling or polishing, shows that the pericarp is nearly all removed, but that the subpericarpal layers are practically unaffected.

Sections of Malay rice present an appearance similar to that of the grain free from husk. The pericarp is removed to a variable extent depending on the amount of pounding and attrition to which the grains have been subjected.

CHEMISTRY OF RICE.

In view of the evidence which shows that the continuous consumption of over-milled rice causes beriberi, and in view of the histological differences between polished and unpolished rices, the suggestion presented itself that by the removal of the subpericarpal layers the grain is deprived of some important nutritive substance or substances.

Chemical analyses have been made of the various kinds of rice with the following average results :—

	Protein per cent.	Fat per cent.	Carbohydrate per cent.	Ash per cent.	Moisture per cent.
Unpolished rice ...	9·0	1·65	75·52	1·08	12·75
Polished rice ...	7·7	0·25	77·23	0·52	14·30
Parboiled rice ...	7·8	0·50	76·88	0·82	14·00
Malay rice ...	7·3	0·63	77·19	0·88	14·00

The average daily ration of an oriental labourer contains 1·3 lb. of rice.

PROTEIN.

Dealing first with the differences in respect of protein, it will be noted that between parboiled and polished rices the difference is small and within the limits of experimental error. Admitting the difference to be a real one, however, and assuming all the protein in rice to be available for purposes of nutrition, a person receiving parboiled rice would consume 9 grains more protein

than one receiving polished rice, and a person receiving Malay rice would consume 36 grains less than one on polished rice. An explanation of the occurrence of beriberi on this basis would therefore not be in accordance with the effects produced.

Fat.

The amount of fat ingested in a ration of 1·3 lb. of rice is 45·5 grains with parboiled rice, 22·75 grains with polished rice, and 57·25 grains with Malay rice. These differences are appreciable and in accordance with the histological findings, but do not appear to furnish an adequate explanation if the fats be regarded merely as the esters of fatty acids.

Carbohydrate.

The differences in respect of carbohydrates are small. Parboiled rice contains more sugar than polished rice or Malay rice, but it did not appear that these differences would furnish an explanation.

Salts.

The ash furnishes a most imperfect idea of the salts contained in rice, all the organic salts being reduced to carbonates, but there is apparently a very constant difference in the amount of ash; it is less in polished rice than in unpolished, parboiled or Malay rices. A person receiving parboiled rice would consume material yielding 74·6 grains of ash, and one receiving polished rice would consume material yielding 47·3 grains of ash. The difference of 27·3 grains is by no means inconsiderable, more especially when it is remembered that small amounts of certain inorganic and organic salts have a great importance in the economy. We were not able to separate out the various salts occurring in the ash of rice.

Poisons in Rice.

White and parboiled rices milled in this country have a common origin in the grain from which they are prepared, and any deleterious substance or substances present in white rice must have developed after milling from the action either of enzymes or of micro-organisms. It has been suggested in this connection that the removal of the pericarp and subjacent layers deprives the grain of protective structures and facilitates the action of micro-organisms.

Rice is washed before cooking, and cooking involves exposure to a temperature of 212° F. or thereabouts for some time; therefore the ingestion of living organisms with the rice may reasonably be excluded. Their activity must be confined to the interval between the milling and the cooking of rice, and the deleterious substance or substances produced must be capable of withstanding prolonged exposure to moist heat.

In our initial experiments for the identification of a poison, white rice was macerated or boiled and macerated, in water acidulated with a small quantity of acetic acid, but on account of the rapid development of moulds in the

mixture and the difficulty of separating the fluid after maceration, these experiments were discontinued.

In the next series of experiments alcohol acidulated with acetic acid was employed. The alcoholic extracts were concentrated *in vacuo* and finally freed from alcohol by exposure in evaporating basins to a moderate heat. The extracts were then examined and tested in every way possible for the identification of poisons. Although numerous examinations and experiments were made no poison was isolated. The failure to obtain a positive result did not exclude a poison, but further work along these lines seemed unlikely to be profitable.

Nutritive Defects of Rice.

We had already noted nutritive differences in the rices which, in the light of our then knowledge, we did not consider adequate to furnish the explanation sought, but failure to obtain a satisfactory result on a poison hypothesis turned our attention to further experiments on the nutritive hypothesis.

Chemical methods having failed, there remained animal experimentation and it was anticipated that by feeding various animals on rice and rice products, information of value might be obtained.

Animal Feeding Experiments.

Eijkman (1897) was the first to observe among fowls kept at the Government laboratory at Weltevreden, Java, spontaneous polyneuritis characterized by degeneration of peripheral nerves and atrophy of the ganglion cells in the anterior cornua of the spinal cord. This condition he attributed to feeding with cooked rice. Experimentally he could produce the disease with decorticated, cooked, and raw rice but could prevent it by the addition of the fine inner capsules of the rice grain, the so-called silver layer (Zilvervliesjes) and could also cure it in the same way. By the administration of different forms of pure starch a similar disease was produced, potato starch was the only one that proved to be harmless. Eijkman was of opinion that a toxic substance, in rice and other varieties of starch, developed in the crops of the fowls. He adds that his investigations show that an apparently physiologically perfect diet can produce severe disease conditions and lead to death.

Eijkman repeated his experiments in Holland and found that the changes in the peripheral nerves were the most important features found on post-mortem examination. They concerned the sensory as well as the motor fibres. They involve bundles of the nerve trunks and present the picture of a non-inflammatory atrophic degeneration such as is seen when a nerve is cut off from its trophic centre. Certain changes in the posterior nerve roots also occur and these likewise show the characters of degeneration and atrophy. The muscles innervated by the affected nerves when treated with osmic acid show a large number of fine fat globules. Feeding with decorticated rice, raw or cooked, and immaterial of the origin or quality of the padi, produced the disease in three or four weeks.

In later investigations Eijkman fed fowls with ground rice and water rolled into balls, and the animals developed polyneuritis. In fowls which died after three and a half months feeding on husked barley he found many degenerated fibres in the sciatic nerve. If fowls were fed on unhusked rice that had been heated in a sterilizer at 115° or 125° C. for two hours the animals developed polyneuritis, after twenty-three days with rice heated to 115° C., and after twenty-one days with rice heated to 125° C. Simple boiling did not destroy the protective value of unhusked rice. Sterilized barley as well as rye and millet acted in the same way as rice.

Grijns (1901) continuing the work of Eijkman found that by adding a certain quantity of *katjang idju* (*Phaseolus radiatus*) to a diet of peeled rice the onset of polyneuritis in fowls was prevented.

Hulshoff Pol (1904) pursuing the line of research suggested by the experiments of Grijns has shown that *katjang idju* has prophylactic and remedial properties in beriberi. He has further shown that a decoction from a moderately large quantity of *katjang idju* possesses the same prophylactic and curative properties as the *katjang idju* itself. Pol considers that an acid ("X" acid) separated from the decoction is the active principle but owing to difficulties in the way of the preparation of this substance no experiments have yet been made with it.

Kiewiet de Jonge (1909) has also tested the value of *katjang idju* as a prophylactic and therapeutic remedy in beriberi. He carried out an admirably planned and extensive investigation in the lunatic asylum at Buitenzorg and fully confirms the work of Grijns and Pol.

Authors' Experiments.

A preliminary experiment was made by feeding fowls on white rice which was known to have been associated with an outbreak of beriberi. A control group was fed on parboiled rice. The fowls were confined in separate cages and were in all respects under identical conditions. The cages were open at the bottom and rested on a hard layer of clay the surface of which was covered with sand; though the possibility of the fowls obtaining such things as worms and the like was not excluded, the conditions were more natural than if the cages had rested on a wooden or concrete floor. In addition to rice which was supplied twice daily at 10 a.m. and 3 p.m. a small tin filled with water was placed in each compartment. The original weight of each fowl was noted and thereafter they were weighed once weekly at 12 noon.

In the group on white rice the first sign of disease was noted on the twenty-sixth day of the experiment. In the morning it was observed that one of the fowls showed weakness of the leg muscles and consequent uncertainty of gait. Instead of standing upright it reclined on its side. When stimulated it would move about in an uncertain way. Examination of the blood failed to reveal the presence of any parasite or other abnormality.

Two days later the paralysis had advanced very considerably. It was

quite unable to walk and the wings were also involved so that these drooped. The diet was now changed to parboiled rice and padi but it was unable to eat, and on the ninth day of the illness the fowl died. At the post-mortem examination no macroscopic change was noted, there was no effusion into the serous cavities and no marked dilatation of the heart. The principal nerves of the legs and wings were preserved and on subsequent examination showed characteristic Wallerian degeneration.

To test whether the disease was a communicable one and unconnected with the diet, a fowl of the parboiled rice group was transferred to the cage occupied by the fowl suffering from polyneuritis on the fifth day of the disease. This fowl was continued on parboiled rice as heretofore and remained healthy at the conclusion of the experiment five weeks later.

A second fowl developed the disease on the twenty-eighth day of the experiment. At 10 a.m. it was noticed to be unsteady but was able to walk about. Two hours later paralysis had extended greatly and the fowl rolled about in the cage in an endeavour to recover the upright position. The head was markedly retracted. The wings were drooping. An attempt was made to feed the fowl with padi but it was unable to eat owing apparently to the spasm of the neck muscles. On the following day the animal died.

This type of case, which was of the convulsive form of polyneuritis of fowls, was not infrequently observed throughout the experiments. It was less common, however, than the type in which simple paralysis was the principal feature (figs. 9, 10).

On the day of onset of the disease a fowl was transferred from the parboiled rice group and placed in the cage to test the possibility of infection. The result in this as in numerous subsequent tests, entirely negatived the possibility of the disease being communicable by contact or through intermediate hosts such as ticks or lice.

Within eight weeks, eight of the twelve fowls had developed polyneuritis. Though the experiment was continued for four weeks longer, the other four fowls remained healthy.

The control group of fowls on parboiled rice originally numbered eight. This number was afterwards increased as fowls from this group were transferred to cages occupied by fowls suffering from polyneuritis. In all, twelve fowls were under observation for periods varying from five weeks to thirteen weeks. At the conclusion of the experiment all remained healthy.

It was thus shown that fowls were sensitive to differences between these two kinds of rice and the occurrence of polyneuritis furnished a reaction which has proved of the utmost value.

In this as in later experiments every possible effort was made to transmit the disease to the fowls of the control groups but with uniformly negative results.

Our previous researches had shown that white rice was either the vehicle by which the agent producing beriberi was introduced into the body or that white rice was deficient in some substance or substances essential for meta-

bolism. Parboiled rice neither conveyed this disease-producing agent nor was it deficient in the substance or substances essential for metabolism.

By following up the results of these initial experiments on fowls we thought that it might be possible to determine the factors of importance in the etiology of beriberi. With poisons it should be possible to remove them from white rice and render it innocuous; with a deficiency it should be possible to remedy it either by the addition of the substances removed in the process of polishing or by the addition of substances extracted from parboiled or unpolished rice.

Is there a Poison in White Rice?

Previous experiments had not been successful in isolating a poison recognizable by chemical means, and inoculation experiments on guinea-pigs, rabbits and monkeys with various substances isolated from white rice had yielded no result.

The disease which occurs among fowls fed on white rice provided a means of carrying out further experiments based on the poison hypothesis. The existence of a poison or poisons in white rice had not at this time been definitely excluded and the further possibility remained that the harmful substance or substances could not be detected by any of the chemical reactions employed. Experiments on fowls were therefore undertaken with products extracted from white rices. In the first of these experiments, white rice from the supplies issued during the inquiry at Durian Tipus was used. The rice was treated in the following manner: 1·5 kilogrammes of finely ground rice were macerated for four days in 1·5 litres of 94 per cent. alcohol. The mass was then transferred to a percolator and percolated with the alcohol in which it had been macerated. The mass was further percolated with 0·5 litre of 94 per cent. alcohol. This operation was repeated three times. After percolation was complete the rice was removed, freed from alcohol by expression, and dried in the sun.

Five fowls were fed on the exhausted rice and three developed polyneuritis within five weeks.

It appeared therefore that percolation with cold alcohol had failed to dissolve out the hypothetical poison.

In a second experiment, rice from the same source was extracted with hot alcohol in the following manner: To 1·5 kilogrammes of coarsely ground rice 1·5 litres boiling 94 per cent. alcohol were added and the rice allowed to macerate for several days. The mass was then transferred to an apparatus for extraction with hot alcohol. This was an enlarged form of Soxhlet apparatus made of copper. The rice was treated in this apparatus by extraction with alcohol for twelve hours. 300 c.c. alcohol were added on two occasions, the further extraction being continued for eight hours. The alcohol was expressed and the rice dried in the sun.

Four fowls were fed on the exhausted rice and two developed polyneuritis. Percolation with hot alcohol had also failed to dissolve out the hypothetical poison.

FIG. 9.—FOWL FED ON SIAM RICE.
Polyneuritis. Mild case. Fifth day of disease.

FIG. 10.—FOWL FED ON RANGOON RICE.
Polyneuritis. Severe case. First day of disease.

A quantity of the extract prepared by means of hot alcohol remained. This alcoholic extract was freed from alcohol by distillation *in vacuo* and by exposure in shallow basins at a low temperature. The alcohol-free extract was emulsified in distilled water and two fowls fed on parboiled rice received in addition daily an emulsion of the extract representing that obtained from 100 grm. of white rice. The experiment was continued for fifty-one days. Both fowls gained in weight and showed no signs of any disease.

These experiments showed that no alcohol-soluble poison was contained in white rice.

In order to control the results of experiments with products obtained by extracting white rices with alcohol, parboiled rices were treated by precisely similar methods to those already described.

In the first of these experiments the product employed was obtained by treating parboiled rice with hot alcohol in an extraction apparatus.

The technique employed in the extraction of rice by this method was as follows:

(1) One kilogramme of rice was ground to a coarse powder and placed in a cylindrical jar. A litre of hot alcohol was poured over the rice and the mixture stirred daily for several days.

(2) The mixture was transferred to a flask of 2250 c.c. capacity and connected up with the extraction apparatus.

(3) After heating for one hour the liquid was aspirated off.

(4) Half a litre of alcohol was added to the partially exhausted rice, the mixture heated as before and the liquid aspirated off. This process was repeated four times.

The exhausted rice was freed from alcohol by exposure to the sun.

The alcoholic extracts contained a quantity of insoluble matter, due to the coarseness of the method by which separation of the menstruum from the marc was effected. No attempt was made to separate the soluble and insoluble substances from these extracts by further filtration, and it is possible that the presence of insoluble substances in the liquid may explain the equivocal results obtained in the extraction of parboiled rice with 94 per cent. alcohol.

In one feeding experiment, parboiled rice which had been ground and afterwards exhausted several times with hot 94 per cent. alcohol, was used. It was anticipated that by this method such substances as lecithin and a portion of other fats would be removed from it. Four fowls only were employed for the experiment. In the fifth week one of them developed a condition indistinguishable clinically from other cases of polyneuritis in fowls fed on white polished rice.

The result indicated that some protective substance ordinarily present in parboiled rice may have been removed by treatment with hot 94 per cent. alcohol. Further experiments were undertaken to test the value of this suggestion.

In the experiments next to be described alcohol of 94 per cent. strength was employed. Of twelve fowls fed on the exhausted rice, two developed

polyneuritis within five weeks and two more in the sixth week. Fowls fed on white rice to which was added the extract from unpolished parboiled rice all remained healthy.

It was concluded from these experiments that the protective substances were soluble in hot alcohol of 94 per cent. strength.

A further experiment was carried out with unpolished parboiled rice extracted with 94 per cent. alcohol. One fowl died in the seventh week. No cases of polyneuritis occurred.

In the control experiment, in which the extracted substances were added to a white rice diet, all the fowls remained healthy.

These latter results can only be explained by assuming that the essential substances were only partially extracted from the parboiled rice.

The next experiment was one in which parboiled rice from the same sample as used in a previous experiment was treated with cold alcohol (94 per cent.) by maceration and percolation. At first five fowls only were employed in this group, but as cases of polyneuritis occurred in fowls fed on white rice treated by identical methods, fowls were transferred to the latter group and continued on the same food to test the possibility of conveying infection. To replace these, fowls were added, and in the course of the experiment eight fowls in all were under observation.

Some of the fowls lost weight, but the general result was a gain in weight, and all remained healthy at the conclusion of the experiment.

It would appear that cold 94 per cent. alcohol is not an effective solvent of the protective substances.

In further experiments parboiled rice was extracted with alcohol of proof spirit strength. The extracts freed from alcohol in the manner already described were used in these experiments.

Twelve fowls were fed on the exhausted rice; three developed polyneuritis within five weeks. In the corresponding experiment, in which the alcohol-free extract obtained from 60 grammes of unpolished parboiled rice was added daily to the diet of twelve fowls on white polished rice, all the fowls remained healthy for five weeks.

This result shows that the essential protective substances are soluble in alcohol of proof-spirit strength.

In this first series of experiments no evidence was obtained that white (polished) rice ever contained a beriberi producing agent. The results taken in conjunction with the histological findings suggested that by the removal of the subpericarpal layers of the grain in the process of milling, the grain is deprived of some substance or substances of high physiological value.

In subsequent experiments this conclusion was abundantly confirmed. In giving a detailed record of these experiments, therefore, these are arranged in accordance with the conclusions ultimately arrived at and not in chronological order. It is hoped that in this way the position will be made clearer.

Experiments with White Rice.

Experiments were carried out with white polished rices from various sources. These may properly be grouped in a single series.

In the first experiment of the series white polished rice used in the inquiry at Durian Tipus was employed. Of the four fowls used for the experiment three developed polyneuritis within four weeks.

The second experiment of the series was one designed to test the effect of feeding fowls on a white polished rice, while at the same time another group was fed on the original partially husked padi and yet another group on white polished rice to which the substances removed in the polishing process had been added. In the group under review, those to which white rice alone was given, one fowl died in the third week without signs of polyneuritis—six others developed polyneuritis within five weeks.

The third experiment of the series was carried out to test whether, as alleged by Braddon, rice that had become stale on account of changes occurring in it in the interval between milling and consumption was more harmful than freshly milled rice. An assistant was stationed in Singapore who forwarded to the laboratory daily by the most expeditious route a quantity of white polished rice milled on the day of despatch. Of twelve fowls fed on this rice five developed typical polyneuritis within four weeks, a result similar to that in experiments in which white polished rice varying in age from a few months to two years was employed.

Other experiments were carried out with white polished rice of the best quality (No. 1 Siam) purchased locally. In one of them nine fowls out of twelve developed polyneuritis within nine weeks, seven cases occurring before the end of the fifth week. In another, eleven cases among twelve fowls occurred within five weeks. It appeared in these experiments that certain fowls were more resistant than others to the injurious influence of white rice. The reason for this was not ascertained though the observation was made that such fowls were commonly the younger members of the group, while those who succumbed most quickly were the full grown fowls who consumed a large quantity of rice. It was also noted that after two or three weeks fowls on white rice usually showed a disinclination to eat.

These observations, which are similar to those made when human beings were under observation, appear to us to be irreconcilable with the idea that simple deprivation of proteins, fats or carbohydrates can be the explanation of the occurrence of the disease.

In every case of polyneuritis Wallerian degeneration was demonstrated microscopically in the affected nerves. The changes are apparently identical in every way with those found in the peripheral nerves in beriberi.

There is evidence that the variety of white polished rice known as Rangoon rice is less harmful than Siam rice. Braddon quotes examples in support of this view and instances have fallen under our own observation.

In some of our experiments Rangoon rice was employed. Two fowls died

in the fifth and fourth week respectively, but there was no clinical or pathological evidence that they suffered from polyneuritis. Both had a form of purulent conjunctivitis.

Another fowl was a typical case of polyneuritis in the fifth week and no other case occurred until the fifteenth week when two others suffered from it. All three cases resulted fatally and the diagnosis was confirmed at post-mortem examination.

Such evidence as is furnished by this single experiment confirms the experience of those who assert the comparative harmlessness of Rangoon rice.

The explanation of this observation is a matter for further inquiry. Whether the padi grown in Burma is richer in protective substances and therefore can afford to lose in the polishing process a greater quantity of them without harmful result, or whether there is some important difference in the milling process it is impossible yet to say. From histological examination of the grains we incline to the former view.

Is Avian Polyneuritis due to Starvation?

It was found that after the first few weeks on a white rice diet, most fowls showed a disinclination to eat. Commonly also, fowls lost greatly in weight before the development of polyneuritis. These were by no means constant features, however, and in some cases fowls continued to eat well and maintain their normal weight until the disease declared itself.

Despite the fact that groups of fowls on a diet of padi, unpolished rice, or parboiled rice, usually continued to eat well throughout, the suggestion was raised that on account of the monotonous nature of a diet of white rice the fowls ceased to eat and that polyneuritis was a result of partial simple starvation. This was at all events a point that required to be tested and accordingly experiments were carried out.

In the first experiment of this series four fowls hitherto fed on padi were employed. Nothing but water was supplied. The bottom of the cage being open they had access to such food, insects and the like, as could be obtained there. This condition of affairs was, however, controlled by the fact that all fowls, including those on white rice, were similarly circumstanced. Within four weeks all the fowls had lost greatly in weight and were weak, but none of the signs constantly associated with polyneuritis had shown themselves. Within a similar period some fowls of a group fed on white polished rice invariably showed signs of polyneuritis.

The number of fowls in the first experiment was, of course, too small to furnish any definite information and a second experiment with twelve fowls was begun. Within five weeks two of the fowls composing this group had died and two others were killed when their condition was such that it was apparent they would die within a few hours. None had showed any clinical signs of polyneuritis and careful examination of the nerves showed no characteristic

degeneration changes. A third experiment was carried out with a similar result.

It was concluded that polyneuritis of fowls is not due to general deprivation of food but to deprivation of some particular element in a diet of white polished rice.

In order to test further the correctness of this conclusion Dr. Fletcher carried out an experiment in which two groups of fowls were fed on white rice.

To the first group 30 grm. of white rice were supplied twice daily in the ordinary way. To the second group 30 grm. of white rice were passed into the crop twice daily.

The result showed that there was no difference between the two groups as to their liability to develop polyneuritis. Polyneuritis therefore cannot be due to simple deprivation of food.

An interesting observation made by Dr. Fletcher in connection with this experiment was this: when a fowl which was being forcibly fed suffered from the disease, the normal digestive powers were markedly interfered with and the crop remained constantly distended with rice. If now a small quantity of polishings was passed into the crop the accumulated rice seemed to be dissolved and normal digestive power was speedily regained.

Experiments with Unpolished Rice.

During the course of the experiments it was observed that fowls always remained in health on padi and that fowls suffering from polyneuritis almost invariably recovered when given padi. In one experiment a partially husked rice, known commercially as "cargo rice," was employed. In this "cargo rice" about half the grains are denuded of husk. This experiment was carried out as a preliminary to certain experiments in which this same product, after milling in various ways, was employed. These latter experiments will be referred to later.

In the experiment now under review, twelve fowls were fed on partially husked rice for six weeks and all remained in good health at its conclusion.

Other experiments in which padi and unpolished rices were employed are detailed elsewhere—all these experiments confirmed the observation that fowls remained in health when fed on rice which still retained its subpericarpal layers.

Experiments with Parboiled Rice.

Experiments with parboiled rice were carried out simultaneously with and for longer periods than experiments with white polished rice, as controls for the results obtained in the latter groups.

The first experiment was one undertaken at the beginning of the series. In it five fowls only were employed. All maintained health and weight during fifteen weeks, cooked unpolished parboiled rice only being supplied throughout.

It was thus shown that, in the conditions under which our experiments were carried out, a diet of parboiled rice and water was sufficient to maintain fowls in health and weight over prolonged periods, and this result repeatedly obtained was regarded as an adequate control to results obtained in shorter periods, five weeks or less, in groups on white rice.

In a second experiment that form of parboiled rice known as *Muthusamba* which is prepared in India was employed; it is an expensive variety of rice eaten only by the more wealthy members of the Indian community. Many fowls in this group showed a moderate gain in weight at the end of six weeks, a few showed a slight loss but all remained healthy throughout.

The next experiment of this series was used as a control to the results obtained in another group of fowls fed on the same sample of rice after exhaustion with proof spirit (in the latter group four cases of polyneuritis occurred within six weeks). In the experiment now under discussion, which was continued for ten weeks, though most of the fowls lost materially in weight and one died in the ninth week, none showed recognisable signs of polyneuritis.

It is apparent from an analysis of the results in this series of experiments that marked differences exist in the nutritive value of different samples of parboiled rice. These differences are due to two factors, the initial richness of the grain and the extent to which the polishing process has been carried out. It does not appear that the method of treatment by parboiling before husking operates in any way other than to harden the external layers of the grain rendering them less easy of removal in milling.

Experiments with Malay Rice.

It is conceded by all those whose knowledge of this country and of its people enables them to speak with authority that among Malays under primitive conditions beriberi is very rare.

Braddon states that "among these natives so long as they lead their primitive pastoral and agricultural life, untouched by the influences which march with a civilization represented by encroaching hordes of Chinese, beriberi never occurs."

Hamilton Wright (1902) says: "My own experience of Malay Kampongs (Malay villages) is that beriberi is almost unknown in them. The farther the Malay population is removed from centres of civilization the less beriberi is seen in it."

Daniels (1906) says "Malays living in Kampongs are the only class that do not suffer from beriberi."

The first experiment in this series was one in which a rice prepared from a locally grown padi was employed. This was obtained from the Kuala Pilah district through the kindness of the District Officer, Mr. Eric Dickson, and Dr. Lucy. A Malay woman prepared rice from this padi after the manner and with the primitive implements used by Malays in their own villages.

Of twelve fowls employed for this experiment all remained healthy with the exception of one which on the forty-second day of the experiment developed polyneuritis. The attack ran the usual course and by treatment with emulsion of rice polishings and padi the fowl recovered completely in six weeks.

In the second experiment in this series, one of a group of experiments to which particular attention will be directed later, Malay rice was prepared from a partially husked padi imported from Indo-China.

As the supply of this product was limited, only eight fowls were employed for this experiment and it lasted only five weeks. All the fowls remained normal throughout.

The occurrence of a case of polyneuritis in a fowl fed on "Malay" rice calls for some comment. It is the single instance throughout these experiments, in which hundreds of fowls have been employed, where polyneuritis developed in a fowl on a diet other than white polished rice. The clinical appearances were in all respects identical with those of other cases of polyneuritis and we do not assign to the case an origin other than dietary. It appears that even the limited amount of polishing to which Malay rice is subjected in its preparation may on occasion be harmful.

Experiments with Rice Meal (Polishings).

As it now appeared that the harmfulness of a rice diet varied directly as the extent to which the rice had been milled, it was determined to test this hypothesis further by adding to a white polished rice, which when given alone had been shown to be harmful, a quantity of polishings equal in amount to that which had been milled away. The miller estimates that from 40 parts of padi he produces 25 parts of rice and 5 parts of polishings. An actual weighing of some thousands of grains of unpolished and polished rice from the same lot of padi showed that the loss in milling was about 10 per cent.

In the first experiment of this series the white polished rice selected was the same as when fed alone had resulted in six cases of polyneuritis among twelve fowls in five weeks. The rice polishings were milled from the same sample. They were sifted in order to remove husks and broken rice and given in the form of an emulsion with distilled water.

During the first and second weeks of the experiment an amount of emulsion equal to 10 grm. of polishings was given daily to a fowl eating 60 grm. of rice. During the third week 8 grm. of polishings were given daily, during the fourth and fifth weeks 6 grm., during the sixth week 4 grm., and during the seventh week 3 grm. were given. Up to the seventh week all the fowls gained slightly in weight. In the seventh week there was a moderate loss amounting to 2·6 grammes per kilogramme of body weight.

It was concluded, therefore, that the amount of polishings necessary to add to 60 grm. of this sample of white polished rice to maintain the normal nutritive equilibrium was between 3 and 4 grm., say 3·5 grm. This amount being added there was in the eighth week a slight gain in weight in the whole group.

It was considered desirable to repeat this result with a rice from a beriberi outbreak. An experiment was therefore planned in which eight fowls were fed on the Durian Tipus rice, each alternate fowl receiving in addition an amount of polishings equal to 3·5 grm. for each kilogramme of body weight.

In four weeks two of the fowls fed on rice alone had developed polyneuritis and all four had lost weight while the four fowls which were given polishings in addition remained healthy and at the end of the experiment all had gained in weight.

The conclusion was now reached that certain essential substances are lacking in white polished rice and that the addition of rice polishings to a diet of white polished rice prevents the occurrence of polyneuritis in fowls.

The Phosphorus Content of Rice.

Having proved that the occurrence of polyneuritis in fowls and of beriberi in man is due to the consumption of rice from which the subpericarpal layers have been removed by the milling process and that such rice is equally harmful whether fresh or stale, we now revert to a consideration of the results obtained from analyses of rices.

Comparing the diet of unpolished rice with that of polished rice it will be seen that there are considerable differences. A diet of polished rice made up with polishings in the amount necessary for the maintenance of weight and health approximates in composition to one of unpolished rice, and it might therefore be inferred that the deficiency of white rice in respect of proteins, fats, and salts was accountable for its harmful results.

The protein content of polished rice differs only slightly from that of parboiled rices which were proved harmless; allowing for experimental errors the differences are apparently insufficient to account for the results. In respect of fat the polished rice is poorer but the difference is small and can hardly account for the difference in the results. The ash gives a very imperfect representation of the salts present but there is a considerable difference in the amount of ash present in the unpolished and polished rices yet even the amount present in the latter rice exceeds that obtained from some parboiled rices.

Now in parboiled rice extracted with hot alcohol the amount of fat removed is relatively great, but of proteins and ash relatively small and in parboiled rice extracted with proof spirit similar results are observed. The proteins were estimated by the Kjeldahl process, and, allowing for the possibilities of experimental error, it must be admitted that the differences in respect of proteins as determined by this method will not explain the results. The question of the carbohydrates cannot seriously be considered, as these were calculated by difference.

These methods of analysis failed in every way to explain the results, and it was necessary to employ other methods. It was suggested to one of us by Dr. Mott that the deficiency of white rice in lipoids might be of importance, and various attempts were made to determine the amount of these present in

rices, but the process was a tedious one and the results not satisfactory. It was decided therefore to estimate the phosphorus pentoxide content of the various rices.

Nearly two hundred estimations have been made and the results recorded on the undried material. The percentage of moisture in various kinds of rice does not vary greatly, being usually from 13 to 14 per cent.

Polished white rice of the kind commercially known as Siam Rice yields an average of 0·26 per cent. of phosphorus pentoxide and is the variety usually associated with severe outbreaks of beriberi. Schaumann gives an analysis of a rice yielding only 0·1 per cent. phosphorus pentoxide. This is lower than any result obtained here.

Polished white rice of the kind commercially known as Rangoon rice yields an average of 0·32 per cent. of phosphorus pentoxide, and the incidence of beriberi is less on this kind of rice than with Siam Rice.

Malay Rice yields an average of 0·38 per cent. of phosphorus pentoxide, and the incidence of beriberi is still less on this kind of rice.

Parboiled Rice yields 0·41 per cent. or over of phosphorus pentoxide and beriberi does not occur when this kind of rice is eaten.

Unpolished rice yields an average of 0·54 per cent. of phosphorus pentoxide and can never produce beriberi.

The great increase in the consumption of parboiled rice in Malaya has induced the local millers to improve the appearance of their product, and this result some of them have sought to achieve by polishing, or as it is technically called, "pearling." Attention has already been directed to the difficulty of accomplishing much in this direction on account of the toughening of the grain by soaking and steaming, but by the use of stone polishers it is possible to remove a considerable amount of the subpericarpal layers with consequent diminution of the phosphorus pentoxide content. We recently examined such a rice which only yielded 0·34 per cent. of phosphorus pentoxide.

Another sample of parboiled rice after hulling yielded 0·60 per cent. of phosphorus pentoxide. After pearling once it yielded 0·50 per cent., and after pearling twice it yielded 0·40 per cent.

An unpolished rice yielding 0·56 per cent. of phosphorus pentoxide was polished in the ordinary way and the polished or white rice yielded only 0·26 per cent.

AVERAGE RESULTS OF ALL ESTIMATIONS.

	Percentage of P_2O_5
Polished rice (Siam)	0·26
Polished rice (Rangoon)	0·32
Malay rice	0·38
Parboiled rice	0·41
Unpolished rice	0·54

Fowls fed on polished rice and polishings in sufficient amount are receiving a diet which approximates in its content of phosphorus pentoxide to a diet of

unpolished rice. The harmfulness of rice is therefore in inverse proportion to its phosphorus pentoxide content and in direct proportion to the extent to which it has been milled.

None of the rices connected with outbreaks of beriberi yielded more than 0·26 per cent. of phosphorus pentoxide. The rices substituted for these and which were effective in stopping the outbreaks yielded not less than 0·40 per cent. of that substance.

Attention should be directed to the percentage of the phosphorus pentoxide in parboiled rice after extraction with 94 per cent. alcohol. The diminution in amount is extremely small, and apparently negatives the vital importance of this substance. In practice extracted rice would never be under consideration. and the value of this estimation as an indicator of the extent to which rice has been polished has stood the test of numerous experiments.

It may be said that the estimation of any of the other constituents of rice would serve equally well for this purpose. It has already been shown that the estimation of proteins is not satisfactory. The removal of the total fats from a rice is an extremely tedious process, and the determination of total ash is complicated by errors of volatilization and incomplete ashing.

Admitting the value of other estimations it must be said that the estimation of phosphorus pentoxide permits of a reasonable margin of error and shows differences which are more striking than in any of the other constituents.

ANALYSES OF RICES.

—	Protein	Fat	Carbohydrate	Ash	Moisture	Percentage of phosphorus pentoxide	Effect on fowls: estimated by the occurrence of polyneuritis
Polishings (rice meal) ..	13·7	14·16	52·77	7·54	11·83	4·1	—
Unpolished rice	9·0	1·65	75·52	1·08	12·75	0·56	—
Polished rice	8·6	0·22	76·23	0·6	14·35	0·26	+
Polished rice (washed) ..	8·2	0·22	75·04	0·84	16·2	0·21	+
Polished rice (washed) plus polishings	8·61	1·29	78·35	0·89	15·86	0·46	—
Parboiled rice	7·55	0·45	77·76	0·94	13·3	0·42	—
The same rice after extraction with 94 per cent. alcohol	7·6	0·06	80·66	0·88	10·8	0·42	+
Parboiled rice	7·8	0·5	76·62	0·78	14·3	0·41	—
The same rice after extraction with proof spirit	7·65	0·10	80·01	0·44	11·8	0·29	+
Siam rice (Depot)	7·8	0·15	77·49	0·56	14·0	0·28	+
Siam rice (D.T.)	7·45	0·17	78·02	0·51	13·85	0·28	+
Rangoon rice	7·3	0·63	77·15	0·74	14·18	0·33	+
Indian rice	6·3	0·2	78·31	0·84	14·35	0·44	—
Malay rice from cargo rice ..	7·7	0·23	75·43	1·14	15·5	0·52	—
Malay rice from Malay padi..	7·2	0·63	77·29	0·88	14·0	0·37	+
Siam rice No. 2 quality stale	7·3	0·40	77·43	0·57	14·3	0·28	+
Siam rice No. 2 quality freshly milled	8·1	0·41	76·76	0·47	14·26	0·27	+
Siam rice No. 1 quality ..	6·9	0·20	77·26	0·40	15·24	0·22	+

ANALYSES OF RICES (CALCULATIONS BASED ON DRIED MATERIALS).

—	Protein	Fat	Carbo-hydrate	Ash	Percentage of phos-phorus pentoxide	Effect on fowls: estimated by the occurrence of poly-neuritis
Polishings (rice meal) ..	15·5	16·0	60·0	8·5	4·6	—
Unpolished rice	10·3	1·89	86·58	1·23	0·64	—
Polished rice	10·0	0·25	89·05	0·7	0·3	+
Polished rice (washed) ..	9·7	0·26	89·64	0·4	0·25	+
Polished rice (washed) plus polishings	10·2	1·53	87·22	1·05	0·55	—
Parboiled rice	8·7	0·51	89·79	1·0	0·49	—
The same rice after extraction with 94 per cent. alcohol	8·5	0·06	90·46	0·98	0·47	+
Parboiled rice	9·1	0·58	89·76	0·56	0·47	—
The same rice after extraction with proof spirit	8·6	0·11	90·79	0·5	0·32	+

The Nature of the Protective Substances.

The results of numerous experiments had made it clear that the addition of rice polishings to a diet of white polished rice prevented the harmful effects of such a diet. In further researches we endeavoured to determine the nature of the substances in rice polishings which were responsible for this result.

In order that the results in various experiments of the series should be comparable it was considered desirable that the various rices and rice products employed should be derived from the same lot of padi. Accordingly we obtained from a rice mill in Singapore these materials in quantity:—

(1) The rice as it passed from the huller to the polishing machines. At this stage the grain is deprived of the husk only (unpolished rice).

(2) The rice after having passed through the polishing machines (white polished rice).

(3) The rice polishings or rice meal collected from the polishing machines.

A preliminary series of experiments was carried out to test the value of these various foodstuffs when fed to fowls.

Unpolished rice sufficed to maintain fowls in good health for many weeks.

With white polished rice within six weeks six fowls out of a total of twelve suffered from polyneuritis.

With white polished rice each fowl receiving in addition 5 grm. of sifted rice polishings daily, all the fowls remained healthy.

This series of experiments confirmed previous results and showed that these materials were suitable for employment in the further researches which it was proposed to undertake.

At this point the various methods of analysis suitable for the recognition of the physiologically active substances were reviewed. The methods hitherto employed for the recognition of specific differences among the various rices and

rice products had always involved the exposure of these materials to high temperatures.

Grijns (1901) in his experiments with *katjang idju*, and Holst and Fröhlich (1907) with various meats and vegetables had shown the harmful effect of exposure to high temperatures on the materials with which they were working. We decided to carry out similar experiments with our own materials.

The first substance experimented with was rice polishings. Quantities of polishings sufficient for six fowls for one day were mixed with water in flasks and heated in the autoclave for one hour at 120° C. A group of fowls on a white polished rice diet were each given daily a portion of the emulsion so prepared equivalent to 5 grm. of polishings. No case of polyneuritis appeared among them in the five weeks during which the experiment was in progress.

In a second experiment polishings heated for two hours at 120° C. were employed. One fowl died in the third week of the experiment without showing the clinical signs of polyneuritis or the characteristic nerve changes on post-mortem examination.

This unexpected result caused us to initiate further experiments to determine whether physical conditions apart from temperature were responsible for this result.

Padi which had been sterilized in a small bag suspended in the wire basket of an autoclave for one hour at 120° C. was employed. One group of fowls were fed on this and another group were fed on the untreated padi. This experiment gave a result identical with that of other observers and showed that when sterilized in an atmosphere of steam for one or two hours at 120° C. the physiological activity of the protective substances was destroyed.

In further experiments padi immersed in water in a porcelain basin and sterilized in an autoclave for one hour at 120° C. was employed. The fowls remained healthy.

With padi sterilized for one hour at 120° C. in a hot-air sterilizer the fowls also remained healthy.

In certain large institutions rice is cooked by steam under pressure. By this method larger quantities are dealt with than by cooking in open vessels and the cooking is more quickly carried out. An opportunity of making a practical test of the relative merits of these two methods of cooking we owe to the courtesy of Dr. J. Gray and Dr. G. D. Freer.

One group of fowls was fed on parboiled rice cooked in the usual way in open vessels. All the fowls remained healthy.

The same rice cooked by steam under pressure as issued to the inmates of a large institution was fed to a second group of fowls. The cooking process involved exposure to steam under a pressure of two atmospheres at 120° C. or thereabouts for two and a half hours. The fowls in this group rapidly lost weight and cases of polyneuritis developed among them.

These experiments showed that physical conditions other than temperature influenced the result. Immersion in water for example in the case of padi seemed to negative the destructive effect of an atmosphere of steam under the

conditions which obtain in an autoclave. This series of experiments was not carried to a conclusion, but there was some evidence that the destructive effect of high temperatures is complicated by the consideration of other physical conditions.

It was evident however that methods of analysis involving exposure of the materials to high temperatures would not enable us to determine the nature of the protective substances and recourse was had to other methods.

Experiments to Identify the Protective Substances.

From this point researches were carried out for the isolation of the substance or combination of substances in polishings which were responsible for protection against beriberi.

For testing the value of the various materials fowls weighing about 1200 grm. were employed. Each fowl, as in previous experiments, was confined in a separate cage. They received rice twice daily, at 10 a.m. and 3 p.m. When receiving polishings, or materials prepared from polishings, the substance in question was given as an emulsion by means of a stomach-tube half an hour after the rice. Every fowl was weighed once a week at 12 noon.

As a result of a series of observations it had been determined that fowls weighing from 1200 to 1400 grm. required about 60 grm. of unpolished rice daily and, if fed on 60 grm. of the polished rice used in these experiments they required in addition 5 grm. of sifted polishings for the maintenance of weight and health.

In a previous experiment where products derived from different lots of padi were employed, 3·5 grm. of the polishings were shown to be sufficient with the white rice then in use. In the present series of experiments all the products, unpolished rice, polished rice, polishings, &c., were derived from the same lot of padi.

For purposes of comparison the following results of analyses are given:—

	Protein	Fat	Carbohydrate	Ash	Moisture	Percentage of P_2O_5
Polishings (sifted) ..	13·7	14·16	52·77	7·54	11·83	4·1
Unpolished rice	9·0	1·65	75·52	1·08	12·75	0·56
Polished rice	8·6	0·22	76·23	0·6	14·35	0·26

When the composition of these articles is calculated on dried materials the differences are rendered more striking and accurate, and when in a similar manner the composition of a diet made up of 60 grm. of polished rice and 5 grm. of polishings is calculated it will be seen how closely such a diet approximates to one of unpolished rice.

Calculated on Dried Materials.

	Protein	Fat	Carbohydrate	Ash	Percentage of P_2O_5
Polishings (sifted)	15·5	16·0	60·0	8·5	4·65
Unpolished rice	10·3	1·89	86·58	1·23	0·64
Polished rice	10·0	0·25	89·05	0·7	0·3
Ration 60 grm. polished rice plus 5 grm. polishings contains per cent.	10·4	1·5	86·3	1·3	0·64

Sifted polishings were invariably employed because polishings as received from the millers contain a considerable admixture of husk and broken rice. Polishings when fresh are neutral in reaction but on keeping they become acid. This change does not impair their efficiency however and polishings which have been stored with ordinary care for months are quite as valuable as the fresh materials. The ordinary process of cooking does not impair the value of polishings. For these reasons it is considered that the essential substance or substances are not unstable.

Experiments to Test the Value of Fats.

Fat in the rice-grain is mostly confined to the subpericarpal layers. Unpolished rice is therefore richer in fat than polished rice and polishings are very rich in fat.

To determine the value of this fat a quantity of sifted polishings was packed in a percolator and percolated repeatedly with petroleum ether. In this way the amount of fat in the polishings was reduced from 14·16 per cent. to 0·6 per cent. The fat-free polishings were dried by exposure to the sun until free from petroleum ether.

Twelve fowls were fed on polished rice and received in addition daily 4·5 grm. of fat-free polishings, the approximate equivalent of 5 grm. of sifted polishings. The fowls remained healthy and maintained their weight just as with polished rice and sifted polishings. The non-importance of fat was therefore determined and its exclusion from the number of possibilities was of the utmost value since the fat had hitherto complicated our experiments.

Experiments with the Substances Soluble in 0·3 per cent. Hydrochloric Acid.

Estimations of the percentage of phosphorus pentoxide in rices had shown its value as an indicator of the liability or otherwise of a given rice to produce polyneuritis. Thus the higher the percentage of phosphorus pentoxide in a rice the less liable was it to produce polyneuritis when fed to fowls.

The unpolished rice employed contained 0·56 per cent. phosphorus pentoxide and did not cause polyneuritis. The polished rice contained 0·26 per cent. phosphorus pentoxide and invariably caused polyneuritis, while washed rice containing 0·22 per cent. phosphorus pentoxide was more harmful than unwashed polished rice. This suggested the probability that the essential substance was one containing phosphorus.

Now it was known that a large percentage of the phosphorus compounds present in rice polishings were soluble in 0·3 per cent. hydrochloric acid. An experiment was therefore carried out to determine if, when polishings were treated with 0·3 per cent. hydrochloric acid, the physiologically active substances were removed.

Polishings in quantities of 180 grm., the amount required by twelve fowls

in three days, were mixed with 1,000 c.c. 0·3 per cent. hydrochloric acid, stirred repeatedly and the following morning filtered through a Buchner's filter. One hundred c.c. of 0·3 per cent. hydrochloric acid were used to wash out the vessels. When fluid could no longer be extracted from the mass it was mixed with 600 c.c. of 0·3 per cent. hydrochloric acid stirred during two hours and thereafter filtered as before.

The extracted polishings were mixed with distilled water, nearly neutralized with sodium carbonate, and the volume adjusted to 1,080 c.c. Thirty c.c. of this emulsion contained 5 grm. of polishings, less the materials dissolved out by the acidulated water.

The combined filtrates obtained from 180 grm. of polishings were nearly neutralized with sodium carbonate and concentrated at a low temperature to a volume of 1,080 c.c. Thirty c.c. of this suspension contained the substances dissolved out by acidulated water from 5 grm. of polishings.

Twelve fowls were obtained and fed on washed polished rice, each receiving daily 30 c.c. of the emulsion of extracted polishings. Cases of polyneuritis occurred. This experiment was repeated with similar results.

Twelve fowls were fed on washed polished rice each receiving in addition 30 c.c. of the suspension of dissolved substances. Cases of polyneuritis did not occur.

When 100 grm. of polishings are extracted in the manner described 26 grm. of solids pass into solution. In this 26 per cent. of the original polishings are contained the physiologically active substances.

Experiments with Phytin.

It having thus been made clear that the substances of physiological importance in polishings were removed unchanged by extracting with 0·3 per cent. hydrochloric acid, the further research consisted in division of this fraction by various methods.

Of the substances contained in rice polishings which are soluble in 0·3 per cent. hydrochloric acid an important constituent is the phosphorus compound phytin. Aron (1910) has claimed that phytin is of value in preventing the onset of polyneuritis in fowls fed on a white rice diet. The results of Aron's experiments with this compound do not appear however to justify the claims that he has made for it.

The quantity of phytin in rice was estimated as follows: a weighed quantity of rice was reduced to coarse powder, shaken with 0·3 per cent. hydrochloric acid and then filtered; the residue was again shaken with acidulated water, this process being repeated until the filtrate ceased to give a precipitate with either copper acetate or alcohol; to the combined filtrates excess of copper acetate was added; the mixture was allowed to stand overnight, thereafter the precipitate was collected, washed, dried and weighed. From that weight, on the assumption that each molecule of the copper phytinate contained two atoms of copper, the amount of phytin was calculated.

The process is not strictly speaking an accurate one but it was the best available and was satisfactory for purposes of comparison between various kinds of rice and their content of this highly phosphorized compound.

The unpolished rice in use was by this method shown to contain 1·07 per cent. of phytin. The same rice after polishing yielded only a trace and the polished rice after washing in water contained no phytin.

Phytin for experimental purposes was prepared by the following method. Sifted polishings were mixed with 0·3 per cent. hydrochloric acid in the proportion of 300 grms. of the former to 2,000 c.c. of the latter, the mixture was stirred throughout the day and on the following morning was filtered through a Buchner's filter. The clear yellowish filtrate was mixed with one and a half times its volume of 95 per cent. alcohol which produced a white precipitate of phytin. The mixture was allowed to stand for a few days, then the precipitate was collected, washed with strong alcohol to free it from acid, and dried in a vacuum desiccator. A friable cake of phytin was obtained readily reducible to a white powder. It was soluble in water, yielding an opalescent solution with an acid reaction and giving on addition of sodium carbonate a white flocculent precipitate.

One hundred grm. of sifted polishings yielded an average of 8·47 grm. phytin. Unpolished rice loses 10 per cent. of its weight in milling and on this basis the percentage of phytin in unpolished rice would be not less than 0·84 per cent. In our experiments to test the value of phytin it was assumed that unpolished rice contained 1·07 per cent. of that substance and any error was in favour of the phytin.

The phytin prepared by us contained 34·8 per cent. of phosphorus pentoxide.

A fowl consuming 60 grm. of unpolished rice daily would receive 0·64 grm. of phytin. A fowl receiving the same amount of washed, polished, and therefore phytin-free, rice would require in addition that amount of phytin daily to bring the value of this diet in respect of phytin up to that of an unpolished rice diet.

Two experiments were carried out with this compound. In the first experiment twelve fowls received washed polished rice and in addition phytin, which was given in the following manner: 9 grm. of phytin were dissolved in distilled water, the solution neutralized with sodium carbonate and the volume made up to 360 c.c. Each fowl received 15 c.c. of this suspension at 10.30 a.m. and 3.30 p.m. daily. All the fowls lost weight and cases of polyneuritis occurred just as if the fowls had received washed polished rice only.

In this experiment the phosphorus pentoxide content of the diet was raised to 0·69 per cent. an amount in excess of that contained in a diet of unpolished rice.

In a further experiment twelve fowls received daily 1 grm. of phytin which was prepared as an emulsion and intimately mixed with the washed polished rice. The results were the same as before.

As shown subsequently, the alcoholic filtrate from which the phytin had

been removed, freed from alcohol, was effective in protecting fowls on unpolished rice from the occurrence of polyneuritis. The importance of phytin was therefore disproved.

As the precipitate, phytin, had been shown to be ineffective, on theoretical grounds it was assumed that the whole of the active substances were contained in the filtrate. The fraction remaining in solution after the precipitation of phytin was next tested.

Polishings in quantities of 180 grm. were extracted with 0·3 per cent. hydrochloric acid, and the combined filtrates were mixed with one and a half times their volume of 95 per cent. alcohol. The precipitate was filtered off. It was found that an average of 8·47 grm. of phytin was obtained from 100 grm. of sifted polishings.

The alcoholic filtrate was then nearly neutralized with sodium carbonate and evaporated at a low temperature until free from alcohol. The residue was diluted with distilled water to a volume of 1,080 c.c. Thirty c.c. of this suspension contained the soluble substances from 5 grm. of polishings.

Two experiments were carried out with this solution. In the first experiment six fowls were fed on washed polished rice, each receiving daily 30 c.c. of the suspension. All remained healthy. In the second experiment with twelve fowls there was a similar result.

That fraction of the substances originally soluble in 0·3 per cent. hydrochloric acid, which still remains in solution on the addition of alcohol, *the acid soluble, alcohol soluble part*, has thus been shown to contain the whole of the substances physiologically active.

An attempt was then made to further divide this fraction by alkalinizing. An experiment carried out with the precipitate, *the acid soluble, alcohol soluble, alkali precipitatable part*, and a second experiment with the filtrate, *the acid soluble, alcohol soluble, alkali soluble part*, had the unexpected result that the substances sought for were found to be no longer physiologically active in either fraction.

Experiments with Proof Spirit Filtrate.

Following on the demonstration that the effective substances in rice meal were contained in the filtrate after precipitation of phytin, and were therefore soluble in alcohol of proof spirit strength, experiments were undertaken with a view to isolating and testing the value of the various substances contained in that solution.

The solution was found to contain substances giving the reactions characteristic of proteins. On increasing the alcoholic strength of this liquid a precipitate was produced, and it was hoped that by sufficiently increasing the amount of alcohol the whole of the protein would be precipitated.

The proof spirit filtrate obtained from 30 grm. of polishings, and measuring from 650 to 660 c.c., was placed in a glass evaporating basin and partially neutralized by means of a normal solution of sodium carbonate. By experi-

ment it was found that 13 c.c. of this solution were required for neutralization of the proof spirit filtrate from 30 grm. of polishings; 10·5 c.c. left the liquid slightly acid, and it was decided that this amount should be added to each quantity of proof spirit filtrate evaporated. The partially neutralized liquid was evaporated at a temperature of 60° C. until free from alcohol.

To the alcohol-free liquid seven times its volume of 95 per cent. alcohol was added, the mixture stirred, allowed to stand for two days, and then filtered. The precipitate weighed on an average 0·7 grm., and consisted partly of phytin; it was freed from alcohol by exposure to the air and suspended in 180 c.c. of distilled water. This volume contained the substances in 30 grm. of polishings soluble in 0·3 per cent. hydrochloric acid, soluble in proof spirit and insoluble in alcohol of 83 per cent. strength.

Six fowls on white polished rice received daily in addition 30 c.c. of this suspension. Cases of polyneuritis occurred.

The 83 per cent. alcoholic filtrate was freed from alcohol by evaporation at a temperature of 60° C., and to the alcohol-free residue distilled water was added to make the volume up to 180 c.c. This volume contained the substances in 30 grm. of polishings soluble in 0·3 per cent. hydrochloric acid, soluble in proof spirit and soluble in 83 per cent. alcohol.

Six fowls on white polished rice received daily in addition 30 c.c. of this solution. Cases of polyneuritis did not occur, and all the fowls remained healthy.

It was thus proved that the protective substances were soluble in 83 per cent. alcohol, and were not inactivated by contact with alcohol of that strength for a period of ten days.

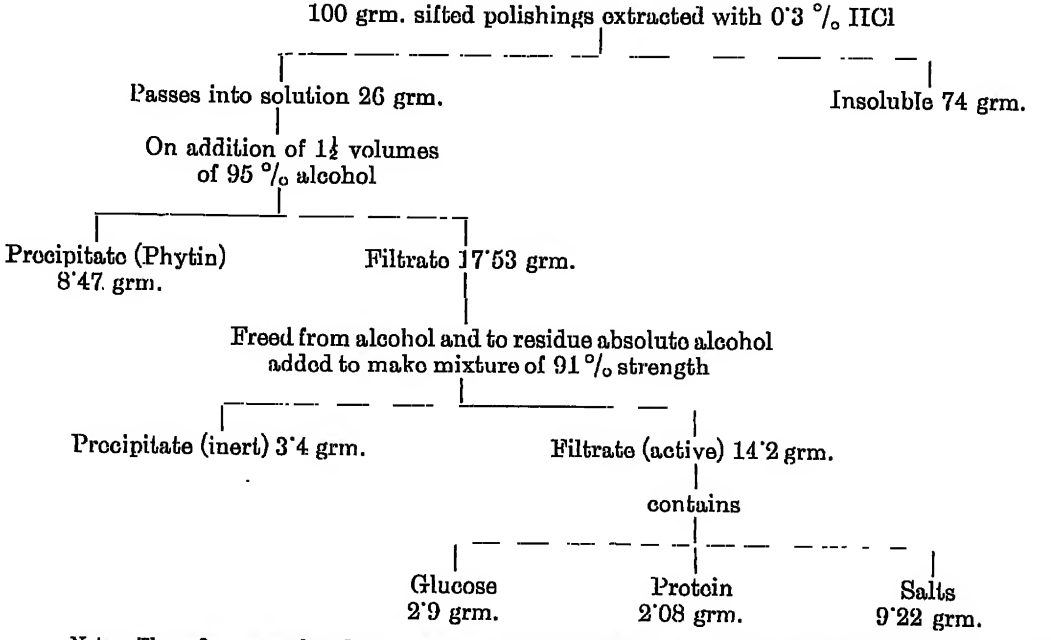
In order that the strength of the alcoholic mixture might be considerably increased, and the volume of the mixture kept within working limits absolute alcohol in place of 95 per cent. alcohol was employed in the next series of experiments. The procedure adopted was as follows:—

The proof spirit filtrate obtained from the 0·3 per cent. hydrochloric acid solution prepared from 30 grm. of polishings, and measuring from 650 to 660 c.c., was placed in an evaporating basin; 10·5 c.c. of normal solution of carbonate of soda was added, and the liquid evaporated at a temperature of 60° C. until the volume was reduced to 50 c.c. To this was added 600 c.c. of absolute alcohol, the mixture stirred, allowed to stand for two days and then filtered. By this method the mixture produced was one containing 91 per cent. of ethyl alcohol.

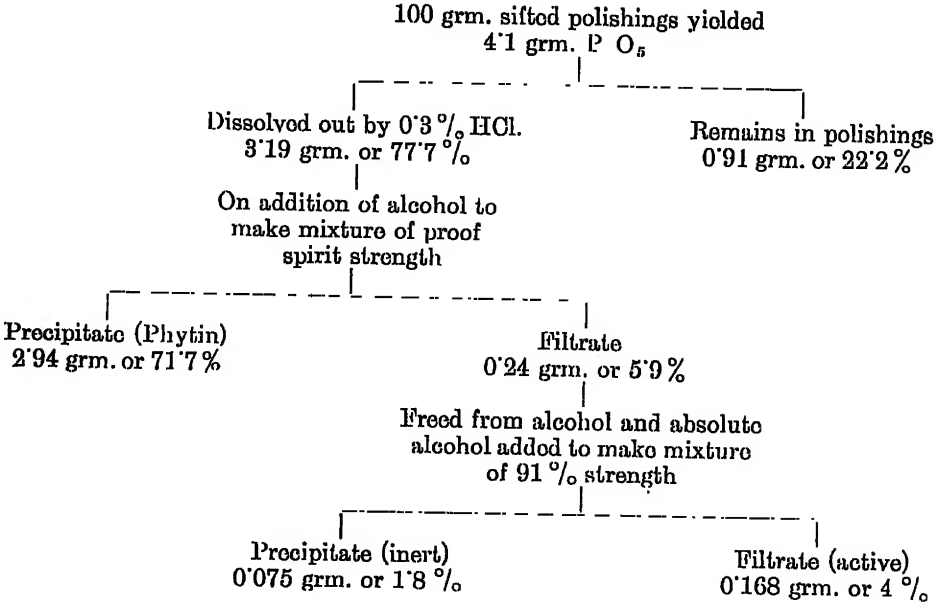
The 91 per cent. alcohol filtrate was evaporated at a temperature of 60° C. until free of alcohol, the residue dissolved in distilled water, and the volume adjusted to 180 c.c. This volume contained the substances in 30 grm. of polishings, soluble in 0·3 per cent. hydrochloric acid, soluble in proof spirit, and soluble in 91 per cent. alcohol.

Six fowls on white polished rice received in addition daily 30 c.c. of this yellowish turbid fluid, and cases of polyneuritis did not occur.

It was thus shown that the protective substances in rice meal are soluble in 91 per cent. alcohol.



Note.—These figures are based on an average of all observations and include many made since the publication of a paper in the *Lancet* No. 4555 of December 17, 1910. They differ to a slight extent from those recorded in that paper.


100 grm. sifted polishings yielded
4·1 grm. P O_5
Dissolved out by 0·3 % HCl.
3·19 grm. or 77·7 %
Remains in polishings
0·91 grm. or 22·2 %
On addition of alcohol to make mixture of proof spirit strength
Precipitate (Phytin)
2·94 grm. or 71·7 %
Filtrate
0·24 grm. or 5·9 %
Freed from alcohol and absolute alcohol added to make mixture of 91 % strength
Precipitate (inert)
0·075 grm. or 1·8 %
Filtrate (active)
0·168 grm. or 4 %

	Effect on fowls; estimated by the occurrence of polyneuritis	Estimated amount in grm. of fat in diet	Estimated amount in grm. of P_2O_5 in diet
Unpolished rice	−	0·99	0·33
Polished rich plus polishings	−	0·83	0·35
Polished rice	+	0·13	0·15
Washed polished rice	+	0·13	0·12
Washed polished rice plus fat-free polishings	−	0·16	0·32
Washed polished rice plus polishings	−	0·83	0·33
Polishings extracted with 0·3 % HCl.			
Washed polished rice plus extracted polishings	+	0·83	0·16
Washed polished rice plus extract	−	0·13	0·28
Extract mixed with one and a-half times its volume of 95 % alcohol			
Washed polished rice plus precipitate	+	0·13	0·27
Washed polished rice plus filtrate	−	0·13	0·13
Filtrate freed from alcohol and absolute alcohol added to residue to make mixture of 91 % strength			
Washed polished rice plus precipitate	+	0·13	0·12
Washed polished rice plus filtrate	−	0·13	0·13

Experiments with 91 per cent. Alcohol Filtrate.

Experiments were undertaken with a view to the isolation and testing of the various substances contained in the 91 per cent. alcohol filtrate.

This filtrate was a clear yellowish liquid. As the protective substance or substances are destroyed by exposure to steam under pressure, it was considered probable that the activity of the liquid was not due to the presence of salts, but rather to the presence of some organic compound or compounds.

When the filtrate is freed from alcohol and the residue mixed with distilled water, a yellowish turbid liquid is obtained. This liquid on saturation with ammonium sulphate yields a reddish brown precipitate which gives the usual protein reactions. Half saturation with ammonium sulphate produces a slight precipitate. Saturation with sodium chloride produces a precipitate, and on filtration the filtrate saturated with ammonium sulphate gives a further precipitate. As many vegetable globulins are not precipitated until their solutions are nearly saturated with ammonium sulphate it cannot be inferred that the alcoholic filtrate contains both a globulin and albumin.

Unpolished rice was tested and found to contain alcohol soluble proteins, while polished rice similarly tested was found to contain none. It would appear, therefore, that Rosenheim and Kajiura were in error in stating that rice did not contain alcohol soluble proteins. It seems probable that they did not examine unhusked rice (padi); unpolished rice was perhaps not available.

The alcohol filtrate was freed from alcohol, and the residue dissolved in distilled water, was tested with Fehling's solution; it gave a precipitate of cuprous oxide. The solution was heated with phenylhydrazine hydrochlorate and sodium acetate; crystals of phenyl-glucosazone were obtained. Another portion of the liquid was saturated with ammonium sulphate and filtered, the filtrate was heated with phenylhydrazine hydrochlorate and sodium acetate and crystals of phenyl-glucosazone were obtained.

The 91 per cent. alcohol filtrate was evaporated to dryness and the residue dried in a desiccator; it was found to contain, after making allowance for sodium chloride formed on partial neutralization with normal solution of sodium carbonate, total solids amounting to 14·2 per cent. of the sifted polishings. These solids form a brown, sticky, hygroscopic residue.

Gravimetrically it was determined that 2·9 grm. of glucose, and by the Kjeldahl process that 2·08 grm. of protein, are contained in this 14·2 grm. of total solids.

It may be that the 91 per cent. alcoholic filtrate contains substances other than proteins, glucose, and salts, but until such time as the various constituents of that filtrate have been isolated, tested, and identified, the biological reaction remains the only method by which the presence of the protective substances can be detected.

Conclusions.

(1) The occurrence of beriberi in the Malay Peninsula has an intimate relationship with the consumption of a diet of which white polished rice forms the staple. Those who consume unpolished rice or slightly polished (native or Malay or parboiled) rice do not suffer from the disease.

(2) Fowls fed on white polished rice known to have been associated with outbreaks of human beriberi develop a form of polyneuritis clearly analogous to beriberi in its clinical manifestations and pathological effects. Other white polished rices produce a similar result. Fowls fed on unpolished rice remain healthy.

These animals may therefore be employed to study the mode of operation by which a diet of white polished rice results in beriberi in man.

(3) The estimation in terms of phosphorus pentoxide of the total phosphorus content of a given rice may be used as an indicator of the extent to which such a rice has been milled or polished, and therefore of its beriberi-producing power when forming the staple of a diet in man.

(4) The harmful influence of white polished rice is not due to the existence in it of a poison developed after milling. White polished rice makes default in respect of some substance of high physiological importance essential for the maintenance of health.

(5) Fowls fed on white polished rice constantly develop polyneuritis in a period of three to four weeks.

(6) If the rice-meal or polishings removed from white rice in the process of milling be added to a diet of white polished rice, fowls remain healthy.

Substances essential for the maintenance of health are therefore contained in polishings.

(7) Unpolished rice which has been submitted to sterilization in the autoclave at a temperature 120° C. for two hours will cause polyneuritis when fed to fowls. The protective substances are destroyed under these conditions.

Methods of analysis involving exposure to high temperatures are therefore unsuitable for determining the nature of the protective substances.

(8) The fats contained in the peripheral layers of the grain are of no value in protecting against polyneuritis.

(9) The protective substances are soluble in 0·3 per cent. hydrochloric acid.

Phytin which comprises 32·5 per cent. of the substances so soluble is without value as a protective.

(10) The substances are not precipitated from solution in 0·3 per cent. hydrochloric acid on the addition of 95 per cent. alcohol in such quantity as to make the resulting mixture of proof spirit strength.

They are soluble in proof spirit, containing approximately 0·12 per cent. hydrochloric acid.

(11) The protective substances are soluble in a slightly acidulated solution, containing 91 per cent. of alcohol, and exclusive of glucose, amount to not more than 11·3 per cent. by weight of rice polishings and not more than

1·13 per cent. of the original unpolished rice-grain. In this fraction are included alcohol—soluble protein and compounds of calcium, magnesium, and phosphorus.

These researches, which comprise an unbroken sequence of experiments beginning with rices associated with outbreaks of human beriberi, demonstrate that rice is rendered harmful by the milling and polishing process to which it is subjected in the preparation of white polished rice. In this process there is removed from the grain some substance of high physiological importance in metabolism, the absence of which results in polyneuritis in fowls and beriberi in man when a diet is consumed of which white polished rice is the staple. Whether these substances act by rendering other elements in the diet available for nutrition or whether they are themselves the nutritive material necessary for nerve tissues can in our present state of knowledge only be matter for conjecture. These substances, small in amount as compared with the total of the diet, have been determined within certain narrow limits, but their exact chemical nature is still unknown.

As measures for the prevention of beriberi in this country, it is recommended that the use of unpolished or under-milled rice be encouraged among those classes of the community in which the disease occurs. The polishing process, if carried out at all, should not extend beyond the removal of the outer skin or pericarp. The parboiling of rice before milling serves the important purpose of so hardening the outer layers of the grain that their removal is less easy and over-milling is less likely to occur. The cooking of rice by steam under pressure should be prohibited. As an indicator of the extent to which rice has been milled, we recommend to chemists the use of the phosphorus pentoxide standard. In the examination of a large number of rices, none was found associated with human beriberi or polyneuritis in fowls which yielded a phosphorus pentoxide content of 0·4 per cent. or over, as estimated on the undried material; the amount of moisture varied only slightly and none of the rices were faced.

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Annual Report, Institute for Medical Research,
for the year 1911.

Beriberi.

In the Annual Report for 1910 an account was given of researches which had been carried out with a view to the isolation and determination of the substance of high physiological importance contained in rice polishings.

It was shown that this substance was soluble in slightly acidulated alcohol, that the percentage of it contained in polishings was extremely small, that exposure to the temperature and for the time required in the ordinary process of rice cooking did not destroy the active substance, but that exposure to steam under pressure did destroy it.

Further work on this subject has been done during the past year. The methods outlined in previous reports were in the first instance employed. The 95 per cent. alcoholic filtrate eventually obtained was freed from alcohol, the residue was mixed with purified sawdust and dried. From the dried mixture by means of various solvents, ether, absolute alcohol and ethyl acetate, attempts were made to fractionate out the active substance, but in no instance was a satisfactory result obtained.

In the next series of experiments an extract was prepared from polishings by means of 94 per cent. acidulated alcohol. In view of the minute amount of the active material contained in polishings, the quantities operated were necessarily large and considerable time was required for the preliminary work. The extract was freed from alcohol by distillation *in vacuo*. Fat was removed from the residual fluid by means of petroleum ether and the fat-free fluid was treated with various precipitating reagents. The precipitates were subsequently freed from the precipitant and their efficiency tested on fowls.

Of the various preparations tested only that obtained by means of phosphotungstic acid proved satisfactory in preventing the occurrence of polyneuritis. The work of isolating the various constituents of the phosphotungstate precipitate has not been completed.

The scientific value of these researches it is not possible at present to estimate, but the results agree with those obtained by other investigators, not only in the field of beriberi research, but in the wider field of research in nutrition and metabolism.

Whether or not it may be possible to prepare a remedial agent for use in the treatment of cases of this disease is a subject which will receive attention in due course.

The pathological researches carried out by Dr. Fletcher, have demonstrated the identity of the nerve changes found in cases of *polyneuritis gallinarum* with those found in cases of beriberi. Proof that the chemical changes met with in the nerve lesions of both these diseases are identical would be of value but is not essential.

Reverting to the practical aspect of this subject, that of the prevention of beriberi, it is satisfactory to find that the conclusions arrived at by us have received confirmation by investigators in most of the countries where this disease occurs. The accuracy of the chemical part of the work has been confirmed by the researches carried out in the Bureau of Science, Manila; the Lister Institute of Preventive Medicine, and the Laboratory of Bio-Chemistry, University of Liverpool.

It may therefore now be considered as beyond dispute:—

(1) That among peoples whose staple of diet is rice, beriberi is caused by the continuous consumption of polished rice and may be prevented by the substitution of unpolished rice.

(2) That a harmless rice becomes a harmful one when cooked by steam under pressure.

It is not anticipated that the application and adaptation of these facts to actual conditions will be rapidly accomplished. Adventitious factors which have been gradually excluded in the course of research will in practice have to be reincluded.

A further outcome of these researches has been to demonstrate the inefficiency of the methods by which dietetic values have hitherto been determined. It is a striking fact, first pointed out by Eijkman, that an apparently physiologically perfect diet can give rise to serious illness and even death. The estimation of proteins by the Kjeldahl process may furnish information of value for purposes of comparison, but the method determines neither the nature nor availability of the proteins. The ignition of a food-stuff and the determination of the ash in no way indicates the nature and composition of the salts originally present in the food-stuff. Substances essential to metabolism we have shown to be capable of approximate but not accurate determination.

The Lancet, October 12, 1912.

The Prevention and Cure of Beriberi.

The Prevention of Beriberi.

In previous communications we have reported the results of our investigations concerning the etiology of beriberi. By an unbroken sequence of observations and experiments, beginning with rices associated with outbreaks of beriberi, it has been demonstrated that rice is rendered harmful by the milling and polishing process to which it is subjected in the preparation of polished rice. In this process there is removed from the grain some substance of high physiological importance, the absence of which results in the production of polyneuritis in fowls and of beriberi in man when a diet is consumed of which polished rice is the staple. Whether this substance acts by rendering other elements in the diet available for nutrition or whether it is itself the nutritive material necessary for nerve tissues can, in our present state of knowledge, only be matter for conjecture.

But the isolation and identification of this substance are matters of scientific rather than of immediate practical importance to those of us who are concerned with the prevention of beriberi, though we are well aware that results may eventually be obtained of much wider significance and importance than can at present be appreciated. The work of other observers has confirmed the accuracy of our researches, and with our present knowledge we are in a position to deal with the question of preventive measures.

Harmless and harmful rices can readily be distinguished by simple inspection, but the definition of unpolished and polished rices on the basis of histological differences alone would not suffice for practical purposes, and it is necessary to have, in addition, a chemical standard. The various constituents of the rice-grain are not distributed uniformly throughout the cells, and it is for this reason that certain of these substances are available for the purpose of a standard or as an indicator of the extent to which the grain has been polished.

The greater part of the fat is contained in the cells of the subpericarpal layers; salts and protein are also relatively more abundant in the cells of the central portion of the grain. It is obvious, therefore, that the estimation of any one of these substances would answer the purpose; the one selected must be suited to rapid and accurate estimation, and there must be such a difference in the amount contained in the two kinds of rice as to allow for a reasonable margin of error.

The extraction of fat from rice is a tedious and troublesome process. The difference in the amount of protein contained in unpolished and polished rices is not sufficiently great to allow of a good margin for experimental error, and the ordinary process of protein estimation is not really an estimation of that substance, but of the nitrogenous constituents of the grain which are capable of being converted into ammonia by a process of reduction.

The estimation of one or other of the inorganic constituents is to be preferred on account of the relative ease and accuracy with which the determination can be carried out. We originally employed the phosphorus content for this purpose, and in all our subsequent experiments and observations have found it in every way satisfactory as an indicator of the extent to which rice has been polished. A safe—or harmless rice—that is, one from which not more than the pericarp or skin has been removed in the process of polishing—will invariably yield more than 0·4 per cent. of phosphorus pentoxide, while a dangerous or harmful rice—that is, one from which the subpericarpal layers have been removed—will yield considerably less than 0·4 per cent.

The standard of 0·4 per cent. of phosphorus pentoxide is therefore not a high one, and the results of its application in practice could not operate unfairly upon anyone. Legislation on the subject of rice in its relationship to beriberi prevention would of necessity demand the incorporation in the enactment of a standard such as this. As already stated, no great degree of skill or training is required to distinguish polished from unpolished rice by simple inspection, but difference of opinion on this point would inevitably occur, and when referred to a court of law the decision would rest on the results of the chemical examination, just as in the case of other food-stuffs, such as milk.

The standard of 0·4 per cent. of phosphorus pentoxide was fixed on the undried material, the percentage of moisture does not vary greatly among different rices, and no apparent advantage would be gained by requiring that the calculation should be based on the dried material.

Chamberlain and Vedder (1911) have recently advocated the estimation of potassium as suitable for standardization purposes. We have had no practical experience of that estimation, but there is no reason why it should not serve the purpose of an indicator quite as well as phosphorus pentoxide, save for the disadvantage which would arise from a lack of uniformity in the standard or indicator employed.

In recommending the adoption of phosphorus estimations for purposes of standardization, it should be clearly understood that we do not thereby subscribe to the view that a deficiency of phosphorus in organic combination explains the production of beriberi by the consumption of polished rice; all the evidence obtained by us is opposed to that view.

The ravages of beriberi always have been, and always will be, greatest among the labouring classes, who prefer polished rice, and whose financial position is subject to fluctuations brought about by economic conditions over which science and medicine have no direct control. So long as these people are in regular employment and in receipt of good wages they can afford to

supplement their rice-ration with other articles of diet, and in this way prevent the occurrence of beriberi. But when adverse conditions prevail, their dietary becomes almost wholly a rice one and soon afterwards beriberi makes its appearance among them.

The use of unpolished rice at all times by these people would prevent the disease occurring among them, but this desirable result will be achieved with difficulty, because to those who have been accustomed to the use of polished rice, unpolished rice has an objectionable appearance. The association of whiteness of food-stuffs with purity has, even in countries other than these, been attended with disadvantageous results. The education of this class of people to the advantages to be derived from the use of unpolished rice must be a slow process, but it is a moot point whether, on the whole, this plan might not prove to be the most successful.

Undue haste in the application of the results of scientific research to practical and actual conditions has so often in the past been attended by unsatisfactory and even disastrous results, that anything in the nature of sumptuary legislation should be introduced only after grave consideration. It has been proposed to make the use of unpolished rice compulsory by legislation. With this object in view it has been suggested that the importation of polished rice should be prohibited, but despotic legislation of this kind would be dangerous, impolitic, and in certain places a serious menace to trade.

Another proposal has been to tax polished rice. Such a tax to be in any way effective would require to be a heavy one and would be most troublesome to apply. If some form of legislation be essential, then, in the conditions in which we find ourselves in the Malay Peninsula, a tax upon polished rice at the point of distribution appears to offer some advantage. To accomplish this it has been proposed to license dealers in polished rice, but it is doubtful if even this method in actual practice would yield results commensurate with the trouble entailed in its application.

It is necessary to emphasize the fact that a harmless rice can be converted into a harmful one by an unsatisfactory process of cooking, and energetic action is required in order to secure the cooking of rice in ordinary pots and to do away with all apparatus in which the rice is cooked by steam under pressure.

The Cure of Beriberi.

Political, commercial, and other difficulties hinder the application of preventive measures, so that even in the most favourable circumstances cases of the disease must continue to occur.

In 1911 there were admitted into the Government hospitals of the Federated Malay States 5,340 cases of beriberi. These cases are almost wholly confined to the Chinese, of whom, according to the census of 1911, there are 433,244. No estimate is possible of the cases which did not seek treatment in Govern-

ment hospitals, but the available information shows that the incidence of this preventible disease was not less than 12·3 per 1,000.

It was therefore desirable to see if a remedial agent could be prepared from polishings. As collected in the rice-mills, polishings are mixed with dust and adventitious substances. The mixture does not look palatable either as a gruel or as an emulsion, and we estimate that an adult accustomed to the use of polished rice would require not less than 1·75 ounces of polishings daily; in this there would be a quantity of substances unnecessary and perhaps undesirable for a sufferer from beriberi. It appeared possible that if the active substances could be separated from the mixture and given in a readily available form, an agent might be obtained which would be of value in the treatment of patients suffering from beriberi.

It by no means follows that the substance, the absence of which from a diet gives rise to disease, will induce recovery in sufferers from that disease. We had noted beneficial effects produced on animals suffering from polyneuritis by the administration of extracts from polishings, and all the evidence showed that the production of beriberi in man and of polyneuritis in fowls was not to be explained by any gross nutritive defect in the ordinary sense of the term, but rather by a deficiency of some substance of whose nature and action we were ignorant.

Believing, as we do, in the clinical and pathological identity of beriberi and *polyneuritis gallinarum*, it was decided, in the first instance, to test the value of the remedial agent on fowls suffering from polyneuritis.

Experiments previously recorded have shown that the active substance is soluble in water and in 91 per cent. alcohol. In alcoholic solution it retains its activity unimpaired for months, and the first test was carried out with an alcoholic extract prepared in the following manner:—

(1) Sifted polishings were packed in a percolator and the fat extracted by means of petroleum ether.

(2) The extracted polishings were freed from ether by exposure to the sun.

(3) One part of fat-free polishings was macerated and frequently stirred in 4 parts of 94 per cent. alcohol acidulated with 0·3 per cent. of hydrochloric acid for one week.

(4) The mixture was filtered and nearly neutralized with sodium carbonate.

(5) The slight precipitate, formed on partial neutralization, was filtered off and rejected. The filtrate was concentrated under reduced pressure (temperature 60° C.) to a small volume.

(6) A little water was added to the residue, and the fat, present in small amount, removed by means of petroleum ether.

(7) The fat-free fluid was concentrated nearly to dryness at a temperature not exceeding 60° C., and the residue dissolved in water and alcohol in such proportion that the final product contained 50 per cent. of alcohol; and 1 c.c. of this fluid represented the soluble materials extracted from 10 grm. of fat-free polishings.

Experiment No. 1

Cases of polyneuritis were obtained in the ordinary way by feeding fowl on polished rice, and as soon as an animal showed distinct evidence of the disease it received the remedial agent; throughout the treatment the fowls were fed on the rice the consumption of which had given rise to the diseases As fowls about to develop the disease and fowls with polyneuritis are averse to the consumption of polished rice, it follows that the test was a severe one. Six cases of polyneuritis (Table I) were treated with the extract.

Table I.—Extract with Acidulated Cold 94 per cent. Alcohol.

No.	Description.	Weight in grammes at commencement of treatment.	1st week.	2nd week.	3rd week.	4th week.	5th week.	6th week.	Remarks.
1	Spotted cock ..	1,060	1,040	1,075	1,120	1,100	1,120	...	Cured after 37 days
2	White and black spotted cock	970	850	...	...	...	...	...	Died 11 days after onset of disease
3	Red cock	940	1,025	1,035	1,067	1,080	...	...	Cured after 32 days
4	White and black spotted cock	1,365	1,470	1,480	1,470	1,460	1,450	1,565	,, ,, 36 ,,
5	Black and red cock..	1,145	1,205	1,215	1,200	1,190	1,180	1,200	,, ,, 36 ,,
6	White and black cock	1,260	1,315	1,380	1,415	1,420	1,445	1,455	,, ,, 40 ,,

No. 1 received twice daily 0·5 c.c. of the extract. A day or two after treatment was commenced the animal regained the power to take rice in adequate amounts, and ten days later its condition was much improved; seventeen days later it was practically well again. After this the remedy was given once daily, and thirty-seven days after the commencement of the illness the animal had perfectly recovered. It was killed, and the nerves on examination showed no signs of degeneration.

No. 2 suffered from a severe attack of the disease with marked retraction of the head, and was obviously very ill. It was given twice daily 0·5 c.c. of the extract, but was unable to eat; this was accounted for by the severity of the attack, its inability to move, and the head retraction. A little rice was therefore pushed into the crop twice daily. Three days later the animal was sufficiently recovered to eat rice voluntarily; seven days later the animal was much better and eating well, but stood with difficulty. The following morning it was found to be very ill and apparently dying, which it did at 2 p.m. Post-mortem nothing of note was observed, but the sciatic nerves showed abundant nerve degeneration.

No. 3 received twice daily 0·5 c.c. of the extract for four days, and subsequently 0·5 c.c. once daily. Sixteen days after the onset of the illness the

animal had almost recovered, and sixteen days later it had completely recovered. It was then killed, and an examination of the sciatic nerves showed no degeneration.

No. 4 received 0·5 c.c. of the remedy once a day. After thirty-six days it had recovered completely, and four days later it was killed; the sciatic nerves were examined and no signs of degeneration were observed.

No. 5 received once daily 0·5 c.c. After thirty-six days' treatment it had apparently completely recovered; four days later it was killed, and a few degenerate fibres were found in the sciatic nerves.

No. 6 received 0·5 c.c. of the extract once daily, and recovery was complete after forty days.

Experiment No. 2.

The next experiment was carried out to test the prophylactic value of this extract. Eight fowls were fed on polished rice, and received daily 0·5 c.c. of the extract. The experiment extended over five weeks. The fowls were in perfect health at the conclusion of the period, and their weights throughout were equally satisfactory. As a control to this experiment, eight fowls on white rice received daily 5 grm. of the same lot of polishings as that from which the extract had been prepared; all of the animals remained healthy.

These experiments demonstrate the value of an extract prepared from polishings as a curative and prophylactic agent.

Experiment No. 3.

In the next experiments more thorough exhaustion of the polishings was aimed at. For this purpose one part of fat-free polishings was mixed with four parts of acidulated 94 per cent. alcohol, and the mixture boiled for one hour under a reflux condenser. The mixture was then allowed to stand overnight, and in the morning filtered; the filtrate was treated in the manner already described, but the final volume was adjusted so that 1 c.c. represented the material dissolved out from 5 grm. of fat-free polishings, and contained 27 per cent. of alcohol by volume. Thus, while increasing the volume of the prophylactic and curative dose the amount of alcohol was not increased. The lower percentage of alcohol was sufficient for purposes of conservation.

Six cases of polyneuritis (Table II) were treated with this extract, of which each case was given 1 c.c. daily. The fowls continued to receive the polished rice on which they had developed the disease.

Nos. 1, 2, 4 and 5 were completely cured in five weeks. No. 6 was cured in forty-four days. No. 3 suffered from a severe attack, and was cured after forty-eight days' treatment. The results are, therefore, quite as favourable as those obtained with the first extract. The extracts prepared by these processes contain less of the non-essential material than can be obtained by any of the other processes we have employed.

Experiments are now in progress with a view to determining if the remedy can be prepared by a less expensive progress, as by employing weaker alcohols

or water. But the less alcohol contained in the menstruum the more saccharine material passes into solution. Whether or not the presence of this substance is disadvantageous we have not yet been able to determine. A watery extract resembling malt extract in appearance and consistence might prove valuable both from the curative and nutritive standpoints. For those cases of beriberi with gastric disturbance it would be desirable to employ an extract containing a minimum of non-essential substances.

TABLE II.—WITH 94 PER CENT. ALCOHOL HOT EXTRACTION.

No.	Description.	Weight in grammes at commencement of treatment.	1st week.	2nd week.	3rd week.	4th week.	5th week.	6th week.	Remarks.
1	Yellow cock	1,200	1,225	1,300	1,315	1,350	1,425	...	Cured after 34 days
2	Brown and black cock.	845	920	945	890	910	920	...	,, ,, 35 ,,
3	Yellow cock	670	670	680	710	700	730	700	,, ,, 48 ,,
4	White and black cock	840	885	880	870	870	870	...	,, ,, 31 ,,
5	Black and white spotted cock	840	885	895	915	845	780	...	,, ,, 30 ,,
6	Yellow cock	990	980	1,025	1,005	995	1,070	1,125	,, ,, 44 ,,

By either of the methods described an effective liquid extract can be prepared, of which a dessert-spoonful represents the material obtained from two ounces of fat-free polishings, the daily dose for an adult suffering from beriberi.

Among the many sufferers from the disease there is, in all probability, a proportion in whom regeneration of the nerves is impossible, but for the others a remedy is furnished which should prove of value in their treatment. Rapid curative effects must not be anticipated, as extensively degenerated nerves require time for their regeneration; but patients placed under favourable conditions and receiving daily, after food, a dose of this extract will have their prospects of recovery enhanced and their period of invalidism lessened.

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The Lancet, January 10, 1914.

The Prevention of Beriberi.

Since the publication of our completed report on the etiology of beriberi in 1912, various communications have been published by investigators who have sought to isolate from rice polishings the substance or substances which are of value in the prevention of beriberi.

We found that by the extraction of polishings with acidulated alcohol a preparation was obtained which was effective in preventing the occurrence of polyneuritis in fowls fed on polished rice and of curing that disease in these animals. It is to extracts prepared by this method or similar ones, for an effective extract can also be prepared by means of acidulated water, that physiological chemists have devoted their efforts.

In this domain much work has been done by Funk who tested the value of the various substances which he isolated on pigeons suffering from polyneuritis induced by the consumption of polished rice. To a curative substance prepared by him he assigned the name "Vitamine," and gave it a formula calculated from the results of a single analysis; this formula he subsequently amended. As the molecular weights are unknown and as in the case of complex substances from the results of a combustion several formulæ can usually be worked out, it is obvious that the formulæ cannot be accepted without question. Moreover, from the variety of formulæ he has given it is suggested that the substances were impure and, but for the fact that he has reduced the volume of the material in which the active substance or substances are contained, a proprietary name might quite as reasonably have been applied to the curative fraction isolated by us and known to be a mixture of substances. Indeed Tsuzuki has applied the name "Antiberiberin" to the moist, black, sticky residue obtained on evaporation of the alcoholic extract.

Reasonable allowances for the magnitude and difficulties of the task confronting physiological chemists must be made, but the methods employed in the work require improvement: those now in use are crude and are sources of errors because of the incomplete separations they effect and because of the decomposition they so constantly produce. It may well be that the substance or substances which prevent beriberi are elusive bodies and may never be isolated in a state of purity, but these problems in no way concern the physician or administrator whose work deals with the prevention and cure of beriberi.

The fact that the continuous consumption of polished rice as the staple of

diet gives rise to beriberi in man, rests on quite other testimony than that derived from experiments on fowls and pigeons and the fact is equally well established that when rice-eaters substitute unpolished rice for polished rice the disease does not occur.

Further valuable confirmatory evidence has recently been obtained from the results of the expedition conducted by Dr. Wollaston and Mr. Kloss into the interior of Dutch New Guinea where they had as their objective the exploration of the Snow Mountains. The task which confronted them was, as both of them well knew, a formidable and an arduous one. Previous experience had shown them that the occurrence of beriberi among them meant failure, thus the Goodfellow expedition of 1909-1911, undertaken to explore the Snow Mountains, was decimated by disease, and Dr. Wollaston, the Medical Officer to that expedition, has recorded that "in the six months from the beginning of June to the end of November, thirty-nine men showed definite signs of beriberi and seven deaths were directly attributable to this cause." The staple of diet was polished rice.

A similar fate befell all previously recorded expeditions into that country save the one conducted by Moszkowski in which unpolished rice was used, but as his expedition only numbered ten men the results were inconclusive.

Convinced, therefore, that the work of the expedition could not be accomplished if their camp-followers and guard were fed on polished rice, Dr. Wollaston and Mr. Kloss decided that only unpolished rice should be used.

Here another difficulty confronted them. The only variety of unpolished rice which can be purchased in the Malay Peninsula in the open market is that known as parboiled rice. To that variety of rice the natives of India who immigrate to this country are accustomed and it is preferred by them. It has, however, an objectionable odour and appearance; irritating properties have been ascribed to it and it has even been thought to predispose to dysentery and the like diseases. Parboiled rice can be prepared free from these objectionable properties, but the manufacturers will not do so and abundant practical experience has shown that the use of parboiled rice is not the solution of the problem of beriberi prevention.

Braddon held that parboiled rice was a preventive of beriberi because it had been "cured," and that white rice was harmful because of some poisonous substance contained in it. The brilliant results obtained by the use of parboiled rice in the Government institutions of Malaya confirmed the accuracy of his view that such rice was a preventive of beriberi, but when we proved that white ice was harmful because in the process of polishing the subpericarpal layers were removed and that parboiled rice was only a variety of unpolished rice, the problem was entirely altered and the prevention of beriberi was established on a rational basis.

Chinese, Malays, Javanese and other rice-eating natives may, when deprived of their liberty in prison, be compelled to partake of parboiled rice, but on regaining their liberty they will not continue its use. If on the other hand an ordinary unpolished rice or "kampong" rice were in use in such places,

a demand would be created for that rice, which would then become available commercially. In this way some real progress might be recorded towards the eradication of a preventible disease.

Fortunately in Java, where the use of parboiled rice is unknown, Dr. Wollaston and Mr. Kloss were able to obtain a supply of unpolished rice adequate for the needs of their expedition. In addition, acting on the suggestion of the writers, they took with them as an additional safeguard a supply of our remedial agent, the use of which we have advocated in the prevention and cure of beriberi.

The expedition consisted of 204 natives of the Malayan Archipelago, who were rice-eaters, together with two Europeans and four Eurasians. They left Batavia about the end of August, 1912, and reached Dutch New Guinea in the middle of September. After reaching the coast, the explorers constructed canoes and ascended the Utakwa river. They went as far as they could go by water, the journey taking two days. They then proceeded overland by stages, each stage occupying three days. Depots had to be constructed at each stage, an undertaking of considerable magnitude which occupied much time. Four and a half months after they had arrived at the coast they reached the Snow Mountains, and then commenced their return journey to the coast which was reached in two months.

The expedition was in all of seven months' duration and, despite the laborious nature of the work, among the 204 rice-eating natives no single case of beriberi occurred. The general health conditions of the expedition are reported to have been excellent.

The daily ration issued to the natives was as follows:—

Rice	700	grm.
Fish or meat on alternate days	150	„
Katjang idju	200	„
Javanese sugar	50	„
Coffee	20	„
Tea	5	„
Salt occasionally	20	„

Two varieties of unpolished rice were used, one with a red pericarp during the first five months and one with a silvery pericarp during the last two months. Neither rice could be considered satisfactory from the cosmetic standpoint. In the case of the red variety only a partial attempt had been made to remove the pericarp and in the case of the silvery variety no attempt had been made to remove this valueless layer of the grain. Despite the appearance no objections were raised by the natives to the use of these rices, but steps ought to be taken to induce manufacturers to remove the pericarp, and so improve the appearance of the grain.

In this connection attention must again be directed to the valueless character of this structure. In previous reports the evidence has been furnished on which this statement is based, but writers, with but one or two notable excep-

tions, refer to the pericarp as the structure whose removal makes the rice harmful, whereas, in fact, it is the removal of the sub-pericarpal layers which is attended with this undesirable result. No real progress in the application of preventive measures can be made until there is available commercially an unpolished rice from which the pericarp has been removed.

Samples of both the rices used were analysed here with the following results :—

	Red variety, per cent.	Silvery variety, per cent.
Protein	9·22	9·41
Fat	1·14	2·10
Carbohydrate	78·64	76·57
Ash	1·06	1·50
Moisture	9·94	10·42
P_2O_5 in Ash	0·54	0·79

It has been consistently advocated that a rice which yields not less than 0·4 per cent. of phosphorus pentoxide may safely be regarded as a harmless one and both of these rices are considerably over this standard, but only in the red variety did any of the grains show a partial removal of the sub-pericarpal layers and in the silvery variety the grain had only been deprived of its husk.

Had the enterprise of manufacturers so far progressed as to remove the pericarp and embryos from these grains, the results would have been equally satisfactory as regards the prevention of disease, the analysis would still have yielded results in accordance with the standard of safety and the cosmetic appearance of the food-stuff would have been greatly improved.

Based on the standards we have previously adopted the ration was ample and the scientific findings are thus in complete accordance with the actual facts. The results of this expedition as regards beriberi are in striking contrast with those which obtained in all previous large expeditions into Dutch New Guinea and, taken in conjunction with the observations and experiments previously recorded by us, the absence of beriberi on this occasion can only be explained in one way—that is, the absence of polished rice from the diet.

In 1909, we demonstrated :—

(1) That beriberi as it exists in the Malay Peninsula is caused by the continuous consumption, as the staple of diet, of rice from which all or the greater part of the sub-pericarpal layers has been removed by the process of polishing.

(2) That a satisfactory measure of the degree of polishing to which a rice has been subjected is the estimation of its total phosphorus in terms of phosphorus pentoxide.

(3) That a rice which yields less than 0·4 per cent. of phosphorus pentoxide cannot safely be permitted to form the staple of a diet in man.

The evidence now submitted is a complete confirmation of the accuracy of

these statements which, as we have repeatedly affirmed, were the logical deductions derived from systematic research.

Writers from Southern Nigeria and Brazil have recently disputed the accuracy of these conclusions, but we are unaware of any systematic observations having been carried out in these countries which would permit of a decided statement being made. When these are made it will be essential to determine that the disease known to them as beriberi is the same as the disease which is known by that name here. After all, beriberi is only a form of polyneuritis and students of this disease know that not only forms of polyneuritis of different origin have been called beriberi, but that diseases of which polyneuritis may not be a prominent feature such as "epidemic dropsy," "Ceylon beriberi" and the like have been included under this name.

We have shown the mode of operation of the factors concerned in the etiology of beriberi as it occurs in the Malay Peninsula. The painstaking researches of Highet and his colleagues have proved that the disease is of similar origin in Siam; and the work of Strong and Crowell has furnished similar evidence for the Philippine Islands. In regard to the Netherlands India these results are in complete accordance with those obtained by the very able Dutch investigators, Eijkman, Grijns and Vordermann, who were pioneers in this field of research.

There is then in the countries mentioned an endemic and epidemic disease which presents certain clinical features and is known to clinicians in these countries as beriberi. For the occurrence of that disease an explanation has been given. The disease can be prevented and, as we have shown elsewhere, may be cured. But, remembering the old adage that "prevention is better than cure," it is necessary to consider the practical application of preventive measures.

While fully appreciating the work of the scientists who seek to advance our knowledge on this subject we must be practical and attempt to reduce, if not abolish, the heavy toll which is yearly exacted by this disease. The determination of exact knowledge is arrived at by processes of abstraction and elimination. In the practical application of that knowledge the disturbing factors have to be reincluded and it is undoubtedly the magnitude of this task which has appalled administrators. But we are unable to convince ourselves that the difficulties are insurmountable. Political and commercial interests have too long been allowed to control the situation. Though such interests cannot be ignored they should not be given undue prominence in the consideration of preventive measures. Resolutions on the subject have been passed on two occasions by the Far Eastern Association of Tropical Medicine, and a resolution in almost identical terms was passed at the recent International Congress of Medicine. These pious expressions of opinion by learned societies in solemn conclave are likely to be and, in point of fact, have been without effect.

We have advocated the preparation of an unpolished rice—that is, a rice from which the husk and the pericarp have been removed and which shall

yield not less than 0·4 per cent. of phosphorus pentoxide. Such a rice can be and has been produced in Siam, but in the absence of a demand its preparation was not continued. The Governments of the countries concerned can create such a demand by making its use compulsory in all gaols and public institutions. In the Malay Peninsula that form of unpolished rice known as parboiled rice is used in practically all such places, but, for the reasons we have mentioned, the use of that rice cannot be extended among the people and an unobjectionable, palatable, unpolished rice must be substituted.

A clause in Government contracts requiring the delivery of an unpolished rice conforming to the standard would give opportunity for observing how such a standard worked in practice, and aid in popularizing a safe and wholesome food-stuff among the people. No one believes that the introduction of such a measure would be accompanied by the immediate disappearance of beriberi, but it is the only way in which progress in its prevention seems possible and it would bring such prevention within the sphere of practical politics.

Annual Report, Institute for Medical Research, for the year 1918.

The Treatment of Beriberi.

In previous annual reports and other publications Fraser and Stanton described a method of preparation of an extract of rice polishings and the favourable results obtained with this product in the prevention and cure of polyneuritis of fowls and in the treatment of human beriberi.

The method of preparation then described involved a number of procedures not easy to carry out except on a small scale in well-equipped laboratories, and in order to obtain a sufficient supply of the extract for a practical test of its value in routine hospital practice the assistance of manufacturing chemists was invoked. In the report for last year the results were recorded of treatment of cases of beriberi by means of these products.

In circumstances arising out of the state of war the transport of materials overseas was interfered with, and it was decided to experiment with simpler methods of manufacture that might enable us to manufacture supplies of the extract locally. These experiments were undertaken in co-operation with Mr. H. Marsden, B.Sc.

(*a*) Preparation of the Extract.

After a series of trials, the details of which it is unnecessary now to record, the following method was devised:—

(1) Rice polishings, preferably fresh from the mill and of the best quality, are sifted to remove portions of husk and broken rice.

(2) 600 grm. sifted rice polishings are mixed with 1920 c.c. distilled water, 480 c.c. 95 per cent. alcohol (Java arrack or a like spirit) and 2·4 c.c. pure hydrochloric acid is added. The mixing is conveniently carried out in upright cylindrical jars of about 3 litres capacity. The fluid is left in contact with the rice polishings for one week, the whole being stirred daily to facilitate extraction.

(3) The fluid is filtered off by means of a Buchner filter funnel under pressure. The residue is pressed to secure a maximum yield of filtrate. The average yield is 2,000 c.c.

(4) The filtrate is then concentrated to about 250 c.c. under reduced pressure and at as low a temperature as is practicable; 75° C.—85° C. appears to leave the anti-neuritic qualities of the extract unimpaired.

(5) The concentrated liquid with the slight precipitate formed on evaporation is made up to 300 c.c., by the addition of 30 c.c., 95 per cent. alcohol and of an appropriate amount of water. This mixture is allowed to stand for a few days and filtered to remove the precipitate. The extract is then ready for use.

(6) One c.c. of this extract represents 2 grm. of the original polishings. It contains 9·5 per cent. alcohol as a preservative.

Trials of the extract so prepared, both experimentally in the cure and prevention of polyneuritis of fowls as well as in the treatment of cases of beriberi in hospital conditions, have shown that its content in anti-beriberi substances is equal to that of extracts prepared by more complex procedures and of theoretically higher value.

(*b*) Test of the Standard Diet.

The following experiment was carried out with fowls to test the standard diet, white polished or over-milled rice and water:—

Experiment I.—*Over-milled Rice and Water only.*

Fowl No.	Original weight grammes	1st week	2nd week	3rd week	4th week	5th week
1	1160	1113	1045	960	825	—
2	1190	1142	1105	1075	—	—
3	1395	1450	1360	1360	1260	1205
4	1449	1322	1180	985	—	—
5	1370	1340	1320	1285	1190	1110
6	1175	1140	995	1045	910	—

Nos. 2 and 4 contracted severe polyneuritis in the fourth week of the experiment, Nos. 1 and 6 in the fifth week. Nos. 3 and 5, though they lost considerable weight remained healthy for five weeks.

(*c*) Tests of the Extract.

Experiment II.—*Over-milled Rice and Water with* 1·0 *c.c. Extract of Rice Polishings passed into the Crop daily.*

Fowl No.	Original weight grammes	1st week	2nd week	3rd week	4th week	5th week
1	1275	1280	1297	1325	1280	1230
2	2232	2230	2230	2295	2200	2130
3	980	980	1010	1055	1030	1045
4	1860	1785	1807	1815	1700	—
5	1215	1217	990	1040	995	985
6	1110	1142	1090	1070	1015	1010

Most of the experimental animals lost weight, and one, No. 4, developed slight signs of polyneuritis in the fifth week. It was concluded that 1 c.c. of the extract, representing 2 grm. of rice polishings, was insufficient. This was only two-fifths of the amount, 5 grm., shown in previous experiments to be required to maintain a fowl of average weight, 1,200-1,400 grm., in health and weight.

It is worthy of note that it was one of the larger fowls, original weight

1,860 grm., that developed polyneuritis. It appears that the "vitamine" intake should bear a direct relation to the carbohydrate intake.

Experiment III.—*Over-milled Rice and Water with 2·5 c.c. Extract of Rice Polishings passed into the Crop daily.*

Fowl No.	Original weight grammes	1st week	2nd week	3rd week	4th week	5th week
1	1330	1310	1300	1290	1305	1300
2	1090	1120	1118	1105	1110	1135
3	1205	1180	1245	1225	1215	1230
4	1062	1055	1050	1050	1030	1010
5	1470	1445	1475	1475	1440	1460

All the fowls remained healthy throughout and nearly constant in weight. 2·5 c.c. of the extract represented 5 grm. of the original polishings, and this experiment confirms the results of many previous experiments, that a fowl of 1,200-1,400 grm. weight can be maintained in health and weight on a diet of overmilled rice if it receives in addition 5 grm. of rice polishings or its equivalent of an efficient extract.

(*d*) Other Dietary Accessories—Tau-geh.

The majority of the cases of beriberi now met with in the hospitals of the Federated Malay States comes from Chinese mining *kongsis*. The staple of the diet of Chinese labourers in mines is almost invariably white over-milled rice and it has been found impossible to induce them to change to parboiled rice, the form of under-milled rices most readily available in normal times in this country.

The work of Axel Holst in Norway and Chick and Hume of the Lister Institute, has shown that the anti-scurvy value of grains is markedly increased after sprouting and that their anti-beriberi value is thereby unimpaired.

Sprouted beans is a usual dietary accessory among the Chinese population under the name *Tau-geh* and among certain sections of the Indian population under the Tamil name *Payattu-mulai*. An experiment was undertaken to test the value of the local market product.

Experiment IV.—*Diet Over-milled Rice and Water. Each Fowl received in addition the Tau-geh derived from 5·0 to 6·0 grm. of "Katjang Idju" (small green beans).*

Fowl No.	Original weight grammes	1st week	2nd week	3rd week	4th week	5th week
1	1300	1390	1380	1325	1315	1330
2	2035	2135	2190	2240	2295	2295
3	1030	1050	1045	1060	1065	1090
4	1045	1150	1155	1155	1165	1205
5	985	1025	1020	1040	1055	1062
6	1055	1135	1165	1190	1210	1240
7	1430	1420	1445	1470	1470	1470
8	1310	1365	1365	1380	1405	1410

All the fowls gained in weight and all remained healthy throughout. At the conclusion of this experiment, three of the animals were continued on

over-milled rice, but without the addition of Tau-geh. These three fowls developed polyneuritis within ten days. The average period of development of polyneuritis on over-milled rice alone where this diet follows one of under-milled rice or the whole grain (padi) is about twenty-five days.

From this result arose the suggestion that the anti-neuritic substances are in some degrees pecific, that is to say if under-milled rice is the staple of the diet the accessory substances should also be derived from rice. This aspect of the matter will be further studied.

(*e*) Treatment of Human Beriberi.

The extract of rice polishings prepared in this laboratory has been issued to hospitals and private practitioners for trial in the treatment of cases of beriberi.

Mr. J. E. Lesslar has made careful observations on the effects of treatment in a series of cases at the District Hospital and Malay Hospital, and reports as follows:—

"During the last quarter of the year the treatment of beriberi with extract of rice polishings prepared in the Institute was tried in 11 cases—nine in the District Hospital and two in the Malay Hospital. The extract was given in half-ounce doses twice daily; this treatment was combined with massage of the limbs with turpentine liniment.

"The results so far have been very satisfactory. Four of the cases showed rapid progress towards recovery. Two recovered more quickly than controls in similar condition on tonic treatment. In three cases progress was more rapid when given extract of rice polishings than on tonic treatment. In one case with a history of alcoholism, improvement was slow. In one patient, who had been in hospital for more than a year, treatment with the extract was without result.

"In one case especially progress was remarkable. This patient, on admission, suffered from general œdema and dyspnœa, and was unable to walk. When the case was first seen, the prognosis was grave, yet within two days the dyspnœa had disappeared, a few days later the œdema had disappeared and the patient able to walk with the aid of a stick. Another case, admitted about the same time with similar symptoms, died on the following day.

"The eleven cases selected for treatment were in different stages of the disease. The duration of the illness, ability to walk, the presence of cardiac symptoms and œdema, were taken into consideration in their selection and in judging the effect of treatment.

"The observations show that the extract of rice polishings is most useful in the early stages of the disease. The earlier the case is treated, the more rapid the recovery.

"In cases of one to three months' duration progress is slow, but when once improvement shows itself, progress is rapid. In cases, ill from four to six months, improvement is uncertain. In cases of six months' duration or more, the extract of rice polishings is useless as a remedy."

ILLUSTRATIONS.

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